Evidence-Based Endocrinology

THIRD EDITION

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The book is dedicated to our spouses—
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the teachers who inspired us; and our fellows,
who taught us so much.

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PREFACE

In 2004, we asked, "Why is there no evidence-based handbook in endocrinology?" Clearly, endocrine disorders lend themselves to evidence-based medicine. They encompass large patient populations: an estimated 14 million persons have diabetes mellitus, an estimated 44 million have osteoporosis or low bone mineral density, and 127 million U.S. citizens are overweight. These diseases are associated with high morbidity and mortality rates, a considerable social price, and high treatment costs.

The endocrine literature is huge and can be overwhelmingly so to a busy clinician. For some disease states, large controlled studies of quantifiable treatment regimens with quantifiable results have been undertaken and published; for other disorders, no such trials are found in the literature, but case studies or small trials of drug therapies or diagnostic measures are available. In the contemporary health care environment, some physicians treating endocrine patients may have little specialized training or experience in endocrine disease and only minimal appreciation of the quality of its vast literature. A manual encapsulating the best available evidence-based information in endocrinology was needed. We therefore set out to publish the first concise handbook that contained the latest clinical trials and evidence. We were gratified that the book was very well received in the United States and internationally, and the readers' feedback was most rewarding.

Given the rapidity and extent of new developments in endocrinology, we are now on the third edition of this book. In *Evidence-Based Endocrinology, third edition*, all chapters received a fresh look from the authors, and hundreds of new references were added. Diabetes and osteoporosis continue to be the most rapidly growing fields, and the authors present a comprehensive update of new therapies for these diseases. The latest clinical guidelines were discussed in chapters on osteoporosis, diabetes, and thyroid disease.

Why should clinicians benefit from this book? At its most basic, it frees them from having to find and digest the huge volume of endocrine literature. The latest and best publications have been sought out and summarized here. At its most useful, *Evidence-Based Endocrinology* may improve diagnosis and treatment of endocrine disorders. Utilizing the 2010 American Association of Clinical Endocrinologists grading system, the contributors have critically assessed and graded studies, assisting the readers in quickly evaluating the articles that have led to practice recommendations. This should allow them to apply the latest and, it is hoped, the best science to the diagnostic and therapeutic aspects of their practice.

It is our hope that readers find the third edition of *Evidence-Based Endocrinology* to be a worthwhile addition to office libraries, to medical reference areas, and, as primarily intended, to the pockets of their lab coats.

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We thank our contributors for their diligence in maintaining focus on their areas of endocrine expertise. Their participation made the editing of this work both fun and exciting. We hope readers will enjoy their efforts and those of the exceedingly helpful and patient professionals at Lippincott Williams & Wilkins.

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In the early years of medicine, patient management was generally based on oral or written strategies gleaned from the interpretation of existing literature or first-hand observation of patients. The results were handed down from "seasoned" or senior authorities to their juniors. Although not uniformly difficult, this form of education certainly had problems. It suffered from the empiric attitudes of some clinicians and their lack of ability or failure to assess current, "best" literature; a bias inherent in the overweighting of the results of limited observations in few patients; often a lack of systematic outcome observation, with failure to include measurements of benefit or harm to patients; and a lack of formal rules to evaluate clinical evidence. In the 1980s, a revolution started that emphasized the quality of evidence in medical decision making [1]. This was founded on two ideas: that more emphasis could be placed on the benefits and risks of therapy and that it was best for patients to use the top therapies from pyramids of research information that contained methodologically weak work at the base to outstanding results at the peak. This latter idea recognized that we could separate gold from junk in medical studies [2] and that some results are more certain than others. All clinical practice guidelines were mandated to rate evidence and grade recommendations based on the strength of supporting evidence.

In the first edition of *Evidence-Based Endocrinology,* we aimed to incorporate rating of evidence to improve the diagnostic and therapeutic decisions offered in the book. In this edition, we decided to utilize the American Association of Clinical Endocrinologists (AACE) 2010 Grading System [3], the same system used in numerous AACE clinical practice guidelines which are all widely read throughout the world (Table 1).

In this book, we have asked authors to grade the references and use the weight of the evidence in making recommendations for diagnosis and therapy throughout the book. Because many areas remain somewhat controversial, authors have been given broad latitude after reviewing literature in their area to make judgments based on their interpretation of all evidence.

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3. **Mechanick JI et al.; American Association of Clinical Endocrinologists.** American Association of Clinical Endocrinologists Protocol for Standardized Production of Clinical Practice Guidelines—2010 update. Endocr Pract 2010 Mar–Apr;16(2):270–283.

Table 1. 2010 American Association of Clinical Endocrinologists Protocol for Production of Clinical Practice Guidelines—Step I: Evidence Rating*

Numerical Descriptor (evidence level)	Semantic Descriptor (Reference Methodology)
1	Meta-analysis of randomized controlled trials (MRCT)
1	Randomized controlled trial (RCT)
2	Meta-analysis of nonrandomized prospective or case-controlled trials (MNRCT)
2	Nonrandomized controlled trial (NRCT)
2	Prospective cohort study (PCS)
2	Retrospective case-control study (RCCS)
3	Cross-sectional study (CSS)
3	Surveillance study (registries, surveys, epidemiologic study) (SS)
3	Consecutive case series (CCS)
3	Single case reports (SCR)
4	No evidence (theory, opinion, consensus, or review) (NE)

*1, strong evidence; 2, intermediate evidence; 3, weak evidence; 4, no evidence.

1

Hypothalamic–Pituitary Disease

Gerald Charnogursky, Nicholas Emanuele, Mary Ann Emanuele, Hong Lee, and Shanika Samarasinghe

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INTRODUCTION OF THE HYPOTHALAMIC–PITUITARY AXIS

The hypothalamic–pituitary unit is a complex neuroendocrine system that is responsible for secretion of anterior pituitary hormones, which are essential for reproduction, growth, metabolic homeostasis, responding to stress, and adapting to changes in the external environment. Each pituitary hormone is secreted in a distinctive pulsatile manner reflecting the interaction between hypothalamic neuroendocrine pathways, feedback effects from peripheral target gland hormones, and intrapituitary mechanisms.

Basal evaluation should consist of anterior pituitary and target organ hormone levels (Table 1.1). Further evaluation depends on the clinical question of hypofunctioning or hyperfunctioning of the suspected endocrine gland. Stimulatory tests provide insight into causes of hypofunction, whereas suppression tests are best if hyperfunction is suspected. Details of the specific evaluation methods of excess and deficiency of each hormone is described with each subsequent clinical entity.

PITUITARY ADENOMAS

Epidemiology and Pathogenesis

Pituitary adenomas can be classified based on size (<1 cm are microadenomas and ≥1 cm are macroadenomas) or functionality (nonsecretory or secretory). Most pituitary tumors are microadenomas and many are nonfunctioning. The prevalence of pituitary adenomas at autopsy is as high as 20% to 25% [1]. The majority of pituitary adenomas occur sporadically. While the most common cause of a pituitary mass is an adenoma, the differential diagnosis includes infiltrative processes, infections, lymphocytic hypophysitis,

Table 1.1. Pituitary and Target Hormones

Pituitary	Target Feedback Hormone	Gland Hormone
Growth hormone	Liver, bone, adipocytes, other tissues	IGF-1
Luteinizing hormone	Gonad	Testosterone (men) Estradiol (women)
Follicle stimulating hormone	Gonad	Testosterone (men) Estradiol (women)
Thyrotropin	Thyroid	T4, T3
Corticotropin (ACTH)	Adrenal	Cortisol
Prolactin	Breast	Unknown

craniopharyngioma, cysts, empty sella, benign and malignant tumors, and metastatic carcinoma [2].

Patients with pituitary adenomas can be asymptomatic or present with symptoms due to mass effect, pituitary hormone dysfunction, or both [2]. Nonfunctioning intrasellar adenomas are often asymptomatic and usually diagnosed incidentally on imaging. The magnitude and severity of symptoms depend on several factors including size, location, and rate of enlargement. In hormone-secreting tumors with associated clinical syndromes, an appropriate hormone assessment will determine the best initial treatment and the need for further therapy. Surgical, pharmacologic, and radiotherapeutic treatments are available for hormone-secreting pituitary tumors.

Patients with large or rapidly enlarging tumors or those with rapid expansion of the contents of the sella have acute onset of signs and symptoms associated with neurologic and/or hormonal dysfunction. This is classically seen in pituitary apoplexy when there is acute hemorrhage or infarction of a preexisting pituitary adenoma (usually a macroadenoma). Patients commonly present with sudden onset of a severe headache, which is usually located in the retro-orbital region. Other symptoms may include nausea, lethargy, altered consciousness, cranial nerve palsies, and visual field defects. Compression of the pituitary gland and its vascular supply can lead to partial or complete hypopituitarism.

Diagnosis

Subsequent sections of this chapter discuss the diagnosis of hyperprolactinemia, acromegaly, Cushing disease (CD), and thyroid-stimulating hormone (TSH)-producing and gonadotropin-producing pituitary tumors. A sellar mass without excess hormone production indicates a nonfunctional pituitary adenoma (NFPA). The α-subunit, common to follicle-stimulating hormone (FSH), luteinizing hormone (LH), and TSH and lacking *metabolic* activity, can be elevated in nonfunctioning adenomas. If initially high, this level can be followed as a marker of tumor recurrence. The β-subunit of these glycoproteins is unique and confers specificity to the hormone.

Treatment

Overview

Tumor type, function, and size determine therapy for pituitary tumors. Initial evaluation should assess the presence and type of hormone hypersecretion, any

hormonal deficiencies and the need for replacement therapy, any visual abnormality, and extrasellar extension. Therapeutic interventions include medical therapy, transsphenoidal or frontal surgery, and radiotherapy. Details of pharmacologic treatment for specific lesions are discussed later in this chapter. Transsphenoidal surgery is indicated in most patients with tumors that secrete growth hormone (GH), adrenocorticotropic hormone (ACTH), and TSH and with large nonfunctional tumors. Radiotherapy, conventional external beam or stereotactic, can benefit patients with significant residual tumor in whom medical and surgical therapy have been unsuccessful. Ideally, excess levels of pituitary hormones normalize, and the hypothalamic–pituitary-target-organ responses, both stimulatory and inhibitory, are restored. Other goals of therapy are relief of headaches and reversal of visual loss.

Surgery

Surgery remains the first-line treatment for symptomatic pituitary tumors with the exception of prolactinomas. Indications include mass effect with visual compromise, primary correction of hormonal hypersecretion, resistance to medical therapy, pituitary hemorrhage/apoplexy, and need for tissue for diagnosis. The most rapid and reliable relief from optic nerve and chiasmal compression is surgery; visual deficits improve in over 85% of patients [3]. Minimally invasive transsphenoidal microsurgery is used in the vast majority of pituitary tumors. This approach precludes invasion of the cranial cavity and manipulation of the brain [4]. Normal pituitary tissue can be clearly distinguished from tumor tissue, facilitating dissection. The mortality in experienced hands is low, between 0.2% and 1% [4]. A transcranial approach is undertaken in tumors with significant temporal or suprasellar extension, especially those contained by a small diaphragmatic aperture (dumbbell configuration), invading into the posterior clivus, or coexisting with intrasellar vascular lesions. An endoscopic approach is increasingly being utilized. Use of an endoscope allows for a superior view of the target area, an enlarged working angle with panoramic views of bony landmarks, and access to tumor extension into the cavernous sinus. Disadvantages include management of perioperative intrasellar bleeding and the requirement for a preoperative computed tomography (CT) scan [3]. Additional advances in the operating room include intraoperative magnetic resonance imaging (MRI) which allows for real-time assessment of the dimensions and extent of the pituitary mass concealed from the operating microscope. Neuronavigation employs a 3D data set provided by preoperative imaging to gain additional anatomical orientation, identifying tumor shape and major arteries superimposed onto the surgical field, and improves the rate of completely excised tumors [4].

In terms of surgical outcomes, the tumor size, magnitude of hormonal hypersecretion, local invasion, previous therapy, and experience of the neurosurgeon are critical factors in determining the likelihood of success. In hormonally active pituitary microadenomas, expert surgeons report remissions in up to 90% of patients [3]. However, with macroadenomas, remission rates vary widely depending on the series and definition of cure.

Because most pituitary tumors are benign, the results of surgery are usually gratifying, particularly in patients with suprasellar extension and visual abnormalities. Improvement in visual field abnormalities occurs in 80% of such patients, progression of visual disturbance is arrested in 16%, whereas visual deterioration occurs in 4% [1]. Prevention of recurrence and avoidance of diabetes insipidus (DI) are perhaps the most challenging goals of pituitary tumor surgery. Surgery provides a complete histopathologic characterization of the lesion. A tissue diagnosis is desirable, since the differential diagnosis of sellar masses

is wide and some lesions can present as pseudoprolactinomas (hyperprolactinemia secondary to pituitary stalk compression or hypothalamic damage, which leads to interference with dopaminergic inhibition of prolactin [PRL] secretion). Craniopharyngiomas demonstrate variable tumor extension; thus, total resection is more difficult to achieve and associated with higher postoperative morbidity.

Postoperative Complications

The low morbidity and mortality associated with transsphenoidal surgery is a major advantage of this approach. Anterior and posterior pituitary dysfunction are assessed after transsphenoidal surgery. Disruption of the hypothalamic–pituitary–adrenal axis (HPA) is covered with perioperative glucocorticoids. Anterior pituitary insufficiency and DI can occur in up to 20% of cases [5]. Monitoring for water imbalances due to deficiency or excess of arginine vasopressin (AVP) requires strict assessment of fluid intake, urine output, and urine osmolality in conjunction with frequent electrolyte measurements. DI is often transient in the postoperative period. Most patients maintain adequate fluid intake and normal volume status. Desmopressin (DDAVP) therapy should be given with caution and is usually only needed briefly. If the patient is alert with intact thirst mechanisms, thirst can be used to guide water replacement. An analysis of 1,571 patients undergoing transsphenoidal surgery demonstrated various patterns of postoperative polyuria and hyponatremia; only 0.9% of patients at 3 months and only 0.25% of patients at 1 year still had polyuria or needed DDAVP [5].

Major neurosurgical complications, including cerebrospinal fluid leak, meningitis, stroke, intracranial hemorrhage, and visual loss are relatively rare (1.5%–4%). Minor complications including sinus disease, nasal septal perforation, epistaxis, and wound issues occur in approximately 6.5% [8]. As transcranial surgery necessitates direct dissection of the brain, vascular structures, and visual pathways, the complication rate is considerably higher.

Mortality rates of 0.86%, 0.27%, and 2.5% have been reported in patients with macroadenomas, microadenomas, and macroadenomas previously treated by other modalities, respectively [4–7]. For patients with previous treatment or macroadenomas, visual loss occurred in 2.5% and 0.1%, leakage of cerebrospinal fluid in 5.7% and 1.3%, stroke or vascular injury in 1.3% and 0.2%, meningitis or abscess in 1.3% and 0.1%, and oculomotor palsy in 0.6% and 0.1%, respectively. The incidence of postoperative hypopituitarism is about 3% in patients with microadenomas, and this increases slightly with size and invasiveness of the tumor. The background rate of pituitary tumor recurrence is about 1% to 2% per year in patients treated by surgery alone; postoperative external pituitary irradiation reduces this level. More recent studies have emphasized the effectiveness of administering radiotherapy after initial surgery to reduce the risk of tumor regrowth in patients with residual mass or hormone hypersecretion [8].

Radiation

Radiotherapy is reserved for patients who have failed surgical and/or medical therapies or who are unable to tolerate surgery due to medical comorbidities. This includes those with persistent or recurrent hormonal hypersecretion states. It is the rational step after failed transsphenoidal surgery in CD as medical therapy is poor. Pituitary irradiation has also decreased the incidence of Nelson syndrome, locally aggressive ACTH-producing tumors due to loss of feedback inhibition at the anterior pituitary ACTH secreting corticotrope in patients who have undergone bilateral adrenalectomy. Postoperative radiotherapy is favored for craniopharyngioma [9].

Radiotherapy has a high therapeutic index, delivering high-energy ionizing radiation to arrest growth of tumor while minimizing exposure to normal

surrounding tissue [10]. The aim is to prevent tumor progression and normalize elevated hormone levels. It is successful in achieving tumor control in up to 95% to 97% of patients at 10 years and 88% to 92% of patients at 20 years. Hormonal control is less successful with 60% to 80% of patients in remission, depending on tumor type after radiotherapy. However, *prompt* reduction in either tumor size or hormone hypersecretion is rare. Reduction in hormone hypersecretion may occur within 3 to 6 months of therapy, but attainment of normal values usually requires at least 5 and often 10 years [11]. Hypopituitarism is the most common complication, with up to 80% of patients demonstrating gonadotroph, somatotroph, thyrotroph, or corticotroph deficits within 10 years after radiation [12]. In one study, half the patients treated with conventional supervoltage radiation developed hypopituitarism within 26 months of therapy [13]. In another series, at least one-third of patients had pituitary deficiencies within 2 to 3 years [14]. The incidence of hypopituitarism increases with length of follow-up, necessitating lifelong monitoring of patients with appropriate hormone measurements and dynamic studies. Other complications of radiotherapy include optic neuropathy (1.5% risk), brain necrosis (0.2%), secondary malignancies such as gliomas and astrocytomas (2%), cerebrovascular disease, and possible cognitive impairment [12]. The development of modern stereotactic technologies that can deliver high-dose radiation more precisely to the tumor can minimize complications and allow for more rapid reduction in hormonal hypersecretion. Stereotactic irradiation can be given as a single-fraction radio surgery using either a cobalt unit (gamma knife) or linear accelerator (LINAC) or as lower fractionated doses over several treatments using a LINAC or proton source [8]. The precision achieved with stereotactic techniques allows for sparing of the normal brain from high radiation doses. The type of radiation treatment administered must be individualized according to the tumor location (proximity to the optic chiasm and cavernous sinus) and the availability of the radiation source. Despite theoretical advantages, long-term outcomes and efficacy have yet to be defined for stereotactic radiation.

HYPOPITUITARISM

Mary Ann Emanuele and Nicholas Emanuele

Pathophysiology

Total or partial hypopituitarism may occur in patients with pituitary adenomas, parasellar invasion, or hypophysitis; after pituitary surgery or radiation (including head and neck radiation for malignancy); or after head injury [15,16]. Pituitary apoplexy resulting from bleeding into an existing adenoma is also commonly associated with hypopituitarism [17]. This can occur postpartum when the pituitary is markedly enlarged, after a complicated delivery with excessive bleeding and hypotension (Sheehan syndrome). In a retrospective 20-year chart review of patients with classical pituitary apoplexy, approximately 90% had permanent hypopituitarism, independent of surgical decompression or not [18]. Other causes of hypopituitarism include compression of normal pituitary tissue (empty sella, suprasellar masses, metastases, and internal carotid artery aneurysm) and infiltrative processes like leukemia, granulomatous disease, or histiocytosis X. Congenital deficiencies of pituitary hormones due to genetic defects can lead to isolated or combined hormone deficiencies and at times are associated with specific syndromes [18].

Deficiency of any or all of the six major hormones (LH, FSH, GH, thyrotropin, corticotropin, and PRL) can occur. The clinical picture will depend on the type, degree, and rapidity of onset of pituitary hormone deficiency (PHD). Most of the

signs and symptoms of PHDs are similar to the hormone deficiencies associated with the target gland failure. In patients with pituitary macroadenomas, 30% or more can have PHDs, with the most common being growth hormone deficiency (GHD). In patients with microadenomas, gonadotropin deficiency is the most common. PRL deficiency is uncommon except with pituitary infarction.

Clinical Findings

Secondary Adrenal Insufficiency

Clinical Presentation

Patients with secondary adrenal insufficiency can present with a wide range of symptoms depending on the degree and duration of ACTH and consequent glucocorticoid deficiency. The symptoms can range from subtle nonspecific symptoms to hypotension and adrenal crisis. Excluding adrenal crisis, patients with secondary adrenal insufficiency commonly report fatigue, weakness, mental dysfunction, dizziness (orthostatic hypotension may be present), anorexia, and weight loss. Women may have decreased libido and lose pubic and axillary hair since the adrenals are the major source of androgen in females. In males, beard and body hair are preserved unless gonadotropin deficiency coexists. Patients with secondary adrenal insufficiency who are not on glucocorticoid therapy are at high risk for adrenal crisis when under increased stress (major medical illness, surgery, etc.) since the pituitary–adrenal axis may not be capable of responding appropriately due to diminished ACTH reserve. Patients with adrenal crisis can present with nausea, vomiting, abdominal pain, severe hypotension, or hypovolemic shock. These patients do not have hyperpigmentation, in contrast to patients with primary adrenal insufficiency (Addison disease) who have hyperpigmentation due to elevated proopiomelanocortin (POMC) and ACTH levels.

Biochemical Diagnosis

Patients have a low cortisol level with low or inappropriately normal ACTH level. Patients usually have normal sodium levels but may have hyponatremia. Cortisol suppresses AVP. With cortisol deficiency, lack of negative feedback on vasopressin secretion allows for increased AVP levels, leading to retention of free water and hyponatremia. Long-term ACTH deficiency leads to atrophy of all zones of the adrenal cortex including the zona glomerulosa, which makes aldosterone. This lack of aldosterone further intensifies hyponatremia. Serum potassium concentration is usually normal in secondary adrenal insufficiency as the renin–angiotensin–aldosterone system is intact (in contrast to primary adrenal insufficiency where there is mineralocorticoid deficiency). However, with long-term ACTH deficiency, atrophy of the entire adrenal cortex can occur with subsequent hyperkalemia. Metabolic acidosis, hypercalcemia, hypoglycemia, normocytic anemia, and eosinophilia may also be present [19].

Measurement of ACTH is required. ACTH is secreted in a pulsatile fashion with a circadian rhythm and increased during stress. ACTH results must be interpreted with knowledge of collection time, clinical stress level, and whether exogenous synthetic glucocorticoids were previously administered. A simultaneous plasma cortisol sample is necessary to interpret the appropriateness of the plasma corticotropin level. An 8 a.m. cortisol between 10 and 20 mg/dl effectively excludes adrenal insufficiency, although patients with secondary (pituitary dysfunction) or tertiary (hypothalamic dysfunction) cortisol deficiency may have low-normal plasma cortisol levels (<3 ng/ml). If clinical suspicion is high, further evaluation with provocative testing should be pursued.

The gold standard for diagnosing secondary adrenal insufficiency is the insulin hypoglycemia test. However, in the acute setting, treatment of patients with

high likelihood of secondary adrenal insufficiency based on history and clinical assessment should not be delayed. Patients can be treated with glucocorticoids, and further testing can be done at a later time [19]. The insulin-induced hypoglycemia test is performed in the morning after an overnight fast. After baseline glucose, ACTH, and cortisol levels are drawn, intravenous regular insulin is given IV push (0.1–0.15 U/kg), and serum (or blood) glucose, ACTH, and cortisol levels are measured at 15, 30, 60, 90, and 120 minutes after the initial bolus. If there is no laboratory or clinical evidence of hypoglycemia (e.g., tachycardia and sweating) after 45 minutes, the insulin should be rebolused and sampling repeated. Adequate hypoglycemia occurs when the blood glucose drops below 40 mg/dl. Clinical manifestations of hypoglycemia and a plasma glucose level below 40 mg/dl are required for the interpretation of ACTH and cortisol levels. If these two criteria are fulfilled, the plasma cortisol level should exceed 20 mg/dl. If this level of cortisol is achieved, the HPA is intact and the clinical syndrome being evaluated is not due to HPA disease. If not achieved, and the basal ACTH level was not elevated, then the syndrome is due to HPA dysfunction. Ischemic heart disease, cardiac conduction disorders, and epilepsy are contraindications to the test.

The corticotropin-releasing hormone (CRH) stimulation test can be used to distinguish between hypothalamic and pituitary causes of secondary hypoadrenalism. An intravenous bolus of synthetic ovine CRH (1 mg/kg body weight or 100 μg total dose) is injected after the patient fasts for a minimum of 4 hours. Blood samples are collected 15 and 0 minutes before and 5, 10, 15, 30, 45, 60, 90, and 120 minutes after CRH injection and analyzed for ACTH and cortisol. A normal response is documented when plasma ACTH increases by at least 35% and/or the serum cortisol increases by at least 20%. Attenuated plasma ACTH and serum cortisol responses to CRH are seen in patients with pituitary ACTH deficiency. Those with hypothalamic disease have exaggerated and prolonged plasma ACTH response and a subnormal cortisol response.

The cosyntropin (synthetic ACTH 1–24) stimulation test bypasses the hypothalamus and pituitary and directly stimulates the adrenals. Therefore, in the strictest sense, this is an adrenal stimulation test. This test and its interpretation are described under the adrenal gland chapter.

An alternative method for testing the HPA axis is the metyrapone test. Metyrapone blocks synthesis of cortisol by blocking 11β-hydroxylase. The induced cortisol deficiency stimulates ACTH production in normal individuals. This ACTH increase leads to an increase in the precursor to cortisol, 11-deoxycortisol (compound S), thus testing the ACTH reserve. Metyrapone 750 mg every 4 hours is given orally for 24 hours. In unaffected patients, it suppresses the 8 a.m. cortisol level to less than 7 mg/dl and increases the serum 11-deoxycortisol greater than or equal to 10 mg/dl. In patients with hypothalamic or pituitary disease, the serum 11-deoxycortisol level is below 10 mg/dl. Hydrocortisone 100 mg should be given intravenously to reverse the cortisol deficiency after the 8 a.m. samples are taken. A shorter version of this test involves the administration of a single metyrapone 750-mg dose at midnight and measurements of serum 11-deoxycortisol and cortisol at 8 a.m. However, this shorter test may not separate normal from abnormal as well as the longer test.

Treatment

Treatment of cortisol deficiency is described in the chapter on the adrenal gland. Every patient receiving adrenal replacement therapy should wear an identifying necklace or bracelet to alert caregivers in the event of medical emergency.

Central or Secondary Hypothyroidism

Clinical Presentation

Secondary or central hypothyroidism (CH) is a rare cause of hypothyroidism characterized by deficiency of TSH. Both primary and secondary hypothyroidism can manifest with the same clinical picture. In CH, symptoms of hypothyroidism tend to be milder than in primary hypothyroidism since there is often some residual TSH secretion [20]. Patients can present with fatigue, cold intolerance, constipation, weight gain or inability to lose weight, dry skin, hair loss, puffiness, nonpitting edema (myxedema), diffuse myalgias exacerbated by exercise, carpal tunnel syndrome, peripheral neuropathy, cognitive impairment, and rarely myxedema coma. On examination, bradycardia and diastolic hypertension (because of loss of the vasodilatory effects of thyroid hormone) can be present, as well as periorbital edema, proximal muscle weakness, and a slow relaxation phase of reflexes. Patients with secondary hypothyroidism do not present with goiter in contrast to those with primary hyperthyroidism [20].

Biochemical Diagnosis

Patients have a low free and total triiodothyronine and thyroxine levels with inappropriately normal or low TSH. If the thyrotropin concentration is normal in association with normal serum thyroid hormone levels, the patient is euthyroid and does not require further testing. If the serum thyroid hormone levels are low and the thyrotropin level is normal (but inappropriately low for the prevailing thyroid hormone levels) or is low, the patient has secondary (from pituitary disease) or tertiary (from hypothalamic dysfunction) hypothyroidism. In the past, pituitary versus hypothalamic failure could be distinguished by administering thyrotropin-releasing hormone (TRH), but TRH is no longer available. Most patients also suffer from other PHDs [26]. CH may be masked by GHD. In one study, 36% of patients with GHD subsequently needed thyroid hormone replacement after GH replacement; the thyroid deficiency was not recognized until after the GH replacement [21].

Treatment

This deficiency is treated with oral levothyroxine 0.075 to 0.15 mg once daily or 1.67 μg/kg body weight daily. The dose is adjusted according to the clinical response, and the serum free thyroxine (free T4) values should be in the middle to upper part of the normal range. Measurement of serum TSH is of no value in assessing a response to levothyroxine in patients with hypothalamic–pituitary disease.

Secondary Hypogonadism

Clinical Presentation

Gonadotropin deficiency, also termed hypogonadotropic hypogonadism, results from either a pituitary defect or a deficiency of hypothalamic gonadotropin-releasing-hormone (GnRH). Acquired causes include acute or chronic illness. The illness may be medical or psychiatric like anorexia nervosa. Acute illness may lead to transient secondary hypogonadism that may reverse weeks to months after the illness resolves. Other causes include use of long-acting GnRH analogs or opiates, which can suppress gonadotropins and long-term use of glucocorticoids [22]. Hyperprolactinemia can affect the GnRH pulse generator and therefore lower LH/FSH production causing hypogonadism. In women, Sheehan syndrome—pituitary infarct due to peri/postpartum hemorrhage—can lead to hypogonadotropic hypogonadism [23].

Secondary hypogonadism can also be congenital. An example of congenital hypogonadotropic hypogonadism is Kallmann syndrome wherein GnRH neurons fail to migrate from the olfactory placode into the hypothalamus during fetal life. Therefore, GnRH is not produced by the hypothalamus, and the pituitary gland is not stimulated to make LH/FSH. Kallmann syndrome can be sporadic or familial (X-linked, autosomal dominant or recessive). Anosmia, midline facial abnormalities, urogenital abnormalities, and synkinesis also can be seen in this disorder [23].

Gonadotropin deficiency often occurs early in the course of hypopituitarism. Hypogonadism is often diagnosed retrospectively after the patient exhibits the symptoms of a mass lesion.

Clinical manifestations of secondary hypogonadism vary, depending on the age of onset. If hypogonadism is present before puberty in men, it can lead to delayed puberty, presence of small testes, small phallus, scant pubic and axillary hair, as well as eunuchoid proportions (disproportionately long arms and legs secondary to delayed epiphyseal closure). There is reduced male musculature, gynecomastia, and persistent high-pitched voice. Men who develop hypogonadism after puberty can present with decreased libido, erectile dysfunction, hot flashes (less common), diminished facial and body hair, fine facial wrinkles, gynecomastia, soft and small testes, progressive decrease in muscle mass, increase in visceral fat, oligo/azoospermia and decreased bone mass [23]. In women, if hypogonadism presents prior to puberty, there can be primary amenorrhea and absent breast development. After puberty, premenopausal women can present with menstrual irregularities, hot flashes, vaginal dryness, dyspareunia, breast atrophy, decreased libido, and low bone density [22].

Biochemical Diagnosis

Gonadotropin deficiency is diagnosed by measuring basal serum LH, FSH, and concomitant gonadal steroids (free testosterone in men and estradiol in women). A low free testosterone or estradiol with low or inappropriately normal levels of gonadotropins is suggestive of hypothalamic–pituitary dysfunction. Usually, dynamic tests are not needed for diagnosis. In males, serum testosterone has a diurnal variation and is higher in the early morning; therefore, blood must be drawn at about 8 a.m. Even though LH and FSH are secreted in a pulsatile fashion in men, levels of these hormones fall within a fairly narrow range. The LH and FSH levels should be interpreted with the clinical findings, simultaneous testosterone level, and possibly semen analysis. In women, marked changes in gonadotropin secretion occur during different phases of the menstrual cycle. Measurement of LH and FSH in a woman who is not taking oral contraceptives and who has regular menstrual cycles is usually not indicated since gonadotropin deficiency is not likely in this clinical setting. Documentation of a normal menstrual cycle and normal luteal-phase serum progesterone level excludes significant gonadotropin dysfunction. In amenorrheic or oligoamenorrhic nonpregnant women, measurement of serum LH, FSH, estradiol, and PRL levels can provide insight into the cause of hypogonadism. Primary ovarian failure presents with increased LH and FSH, whereas hypogonadism due to pituitary or hypothalamic causes have low estradiol and low or inappropriately normal LH and FSH levels.

Treatment

Treatment of hypogonadism is described in the chapter on reproduction.

Growth Hormone Deficiency

Clinical Presentation

GHD in children results in growth failure. However, symptoms of GHD in adults are nonspecific, and evaluation for this disorder is usually performed in adults

with a history of GHD in childhood or known pituitary disease. GHD is likely if the patient has documented deficiency of other pituitary hormones including TSH, ACTH, and gonadotropins [1]. In adulthood, GHD can present with reduced energy and depressed mood. GH-deficient subjects have a diminished sense of physical and psychological well-being (e.g., less energy, emotional lability, sense of social isolation, and diminished libido). GH lack contributes to decreased lean body mass and increased abdominal adiposity. Exercise capacity is impaired and there is decreased muscle mass and muscle strength. The contractile properties of muscles are affected in patients with GHD [24]. Fracture risk is increased since bone density, particularly in the lumbar spine, is reduced in some patients with adult-onset GHD. Levels of serum low-density-lipoprotein (LDL) cholesterol may be increased, whereas high-density-lipoprotein (HDL) cholesterol remains normal. Deficiency of GH may contribute to the increased cardiovascular mortality found in patients with hypopituitarism who receive replacement hormones other than GH.

Biochemical Diagnosis

Since GH is secreted in a pulsatile manner, a random GH level is not helpful in the diagnosis of GHD. GH values in a normal individual may vary from undetectable (during an interpulse interval) to more than 40 mg/l. GH secretion is affected by food ingestion; it is suppressed by hyperglycemia and stimulated by amino acids and hypoglycemia. Slow-wave sleep is also associated with increased GH secretion. Insulin-like growth factor-1 (IGF-1, previously termed somatomedin C) is a more reliable screening test for GHD. The synthesis of IGF-1 is GH dependent. It is easier to interpret the age- and gender-specific IGF-1 level given its longer half-life and more steady blood level. A serum IGF-1 concentration below the age- and gender-specific lower limit of normal in a patient who has pituitary disease supports the diagnosis of GHD [2].

If one suspects GHD, a stimulation test is required. Provocative tests of GH secretion include insulin-induced hypoglycemia and arginine (ARG) combined with levodopa (L-DOPA) [25,26]. Of these, insulin-induced hypoglycemia is most commonly used and has been described earlier in this section.

In the ARG/ L-DOPA test, L-DOPA 500 mg PO is given at the start of the infusion of ARG 30 g in a 10% solution over 30 minutes. Blood is obtained 0, 30, 60, 90, and 120 minutes for GH, and a serum GH less than or equal to 1.5 μg/l provides 95% sensitivity and 79% specificity for the diagnosis of GHD. A lowered target GH 0.25 μg/l improves specificity to 95% but lowers sensitivity to 75%. Weaker stimulation tests include ARG, clonidine, or L-DOPA alone. All tests of GH secretion are more likely to give false-positive results in obesity. All the tests are performed in the morning after an overnight fast.

Treatment

GH is most often given as a daily subcutaneous injection at bedtime. The recommended starting dose for adults is 0.006 mg/kg/d with a maximal dose of 0.0125 mg/kg/d. Dosage adjustment is based on the clinical response and the normalization of IGF-1 matched for age and gender. Use of GH replacement is not associated with an obvious early increase in the rate of hypothalamic or pituitary tumor recurrence if pituitary radiation is given postoperatively. GH replacement increases lean body mass, decreases fat mass (particularly abdominal fat), increases bone density, and increases serum HDL levels. Improvement in exercise tolerance, muscle strength, psychosocial assessments, and mortality related to cardiovascular disease has been observed in adults with hypopituitarism that has been treated with GH [24]. An open clinical trial assessing carotid artery intimal wall thickness (IWT) in GH-deficient adults demonstrated a potent

inhibitory effect of 1-year GH replacement on IWT progression, which was maintained after 2 years [27]. The rapid effect of GH replacement on IWT may indicate a beneficial effect of GH treatment on the vascular system. The most common side effects of GH include fluid retention, carpal tunnel syndrome, and arthralgia; these side effects are usually dose related and disappear with dose reduction [28]. The contraindications for GH use include malignancy and diabetic retinopathy.

Prolactin Deficiency

PRL is the only pituitary hormone that is under tonic inhibition (via dopamine); PRL deficiency is rare and it tends to occur in conjunction with other PHDs. The main clinical presentation of PRL deficiency is inability to lactate in women.

Treatment

Hormone replacement is possible for all the target organ hormones (e.g., cortisol, thyroxine, estrogen, and testosterone) and some of the pituitary hormones (e.g., gonadotropins, GH). Replacement must be tailored to the individual hormone deficiency and, if possible, it should not be instituted until the hypothalamic–pituitary–target organ axis has been assessed. For example, thyroid hormone replacement before institution of glucocorticoid therapy in a patient with cortisol deficiency may precipitate adrenal crisis.

Prolactin

Measurement of a random serum PRL level is useful if the level is unmeasurable or markedly elevated. An unmeasurable level may suggest hypopituitarism. Although PRL concentrations vary during the day, being lower in the afternoon, the time of sampling is usually not critical.

Pituitary Hormone Excess

Thyrotropin Excess

Clinical Presentation

TSH-secreting tumors comprise less than 2% of all pituitary tumors, and most patients have the typical symptoms and signs of hyperthyroidism with diffuse goiter in 95% and visual field defects in 40% [30]. About 25% of patients have cosecretion of other pituitary hormones, usually either PRL or GH. Because of this cosecretion, patients may exhibit galactorrhea and/or the features of acromegaly in addition to hyperthyroidism.

Biochemical Diagnosis

The characteristic thyroid function tests in these patients are normal or high serum TSH with elevated free T3 and free T4 concentrations. Up to 30% of patients will have TSH values within the normal range. It is important to remember that the differential diagnosis of high circulating thyroid hormones with nonsuppressed TSH includes syndromes of resistance to thyroid hormone as well as interferences in either or both the TSH and thyroid hormone assays. The most common cause of the combination of high thyroid hormones and nonsuppressed TSH was interference in the free T4 assay. To determine if this is the case, a free T4 by equilibrium dialysis should be obtained. If the result is normal, then assay interference is the likely cause. If not normal, then the much less common conditions of TSH-producing pituitary tumor (TSHoma) or thyroid hormone resistance need to be considered, and the two must be distinguished. Compared to patients with thyroid hormone resistance, those with TSHomas are more likely to be clinically hyperthyroid, have increased levels of α-subunit (TSH is a heterodimer comprised of a common α-subunit and a unique β-subunit),

have high sex hormone–binding globulin (a thyroid hormone–dependent protein and thus a measure of the tissue effect of thyroid hormone), and have a pituitary lesion identified by sellar MRI. Furthermore, exogenous administration of T3 (80–100 μg/d for 8–10 days) may suppress TSH in those with hormone resistance but not in those with TSHomas. This test is contraindicated in elderly patients or in those with coronary disease. People with TSHomas do not have a TSH response to TRH, another distinguishing feature from hormone-resistant states. However, TRH is no longer available for general clinical use. Since the hormone resistance syndromes are inherited, there may be a family history.

Treatment

The primary treatment for TSHomas is surgery. If surgery is contraindicated, radiotherapy can be considered. However, experience with somatostatin analogs (SSAs) or dopamine receptor agonist is promising since many TSH-producing pituitary tumors have somatostatin and/or dopamine receptors. After therapy, there may be transient or permanent CH [29].

Nonfunctional Adenomas and Gonadotropin-Producing Adenomas

Overview

Nonfunctional pituitary adenomas (NFPAs) were classically subdivided as gonadotropin-producing adenomas, null cell adenomas, and oncocytomas based on structural and immunohistochemical characteristics [30]. Gonadotropin-producing adenomas stain positively for FSH, LH, and/or their subunits (LH and FSH are heterodimers comprised of a common α-subunit and a unique β-subunit), whereas null cell adenomas and oncocytomas have negative hormonal staining. Gonadotropin-producing adenomas, null cell, and oncocytomas account for about 85% of operated nonfunctioning pituitary adenomas. The remaining 15% are silent adenomas, which express hormones as detected by immunocytochemistry but do not secrete them and thus do not lead to hormone-related clinical symptoms. Most oncocytomas and null cell adenomas belong to the gonadotropin-producing adenoma family, since they express steroidogenic factor 1 (SF-1), a transcription factor whose pituitary expression is specific to the gonadotrope cell lineage. So, despite the negative staining for gonadotropins, these tumors have been shown to secrete LH, FSH, and a-subunits in vitro.

Clinical Presentation and Biochemical Diagnosis

Gonadotropin-producing adenomas usually come to clinical attention as macroadenomas when they cause neurologic symptoms. They may also be found on imaging for an unrelated reason. Impaired vision is the most common presenting symptom, caused by suprasellar extension of the adenoma compressing the optic chiasm. Other presenting neurologic symptoms include headache, diplopia, cerebrospinal fluid rhinorrhea, and pituitary apoplexy induced by sudden hemorrhage. Importantly, apoplexy can be precipitated by administration of a drug that stimulates gonadotrope adenomas, such as GnRH analog treatment of prostate cancer.

Hormonal deficiencies can also be the initial presentation. These are due to compression of nonadenomatous pituitary cells by the macroadenoma and by mechanical compression of portal vessels and pituitary stalk. This stalk compression leads to diminished delivery of hypothalamic hormones and dopamine to pituitary cells. The decrease of hypothalamic hormones may lead to deficiencies of most of the anterior pituitary hormones. In contrast, the decreased delivery of dopamine, an inhibitor of PRL secretion, causes an increase in circu-

lating PRL. This increased PRL in the context of a non-PRL-secreting pituitary tumor is termed pseudoprolactinoma. The diagnosis is established by finding abnormalities of the subunits of LH and FSH that are characteristic of a gonadotrope adenoma and follow-up imaging by sellar MRI.

The least common clinical presentation is one that results from hormonal abnormalities, as gonadotrope adenomas are hormonally inefficient and the LH and FSH produced are usually not sufficient to result in hormonal derangements. Also, only about 35% of these tumors secrete enough gonadotropins to raise the serum levels [31], and the hormone combinations differ in men and women. In men, an elevated basal serum FSH concentration with an intrasellar mass lesion usually indicates that the lesion is a gonadotrope adenoma. The diagnosis is strengthened if the patient also has a supranormal level of the free α-subunit and serum LH accompanied by an elevated testosterone level. In women, recognizing the gonadotrope origin of an intrasellar mass on the basis of serum intact FSH and LH is more difficult, especially in menopausal woman. However, a gonadotrope adenoma is suspected if there is a markedly elevated FSH level associated with a subnormal LH concentration, as this pattern is not likely in the postmenopausal state or in premature ovarian failure. An elevated serum free α-subunit concentration is also helpful. An elevated serum estradiol with an FSH concentration that is not suppressed associated with endometrial hyperplasia and polycystic ovaries by ultrasound in a woman of premenopausal age who presents with amenorrhea or oligomenorrhea strongly suggests a gonadotrope adenoma–secreting FSH and causing ovarian hyperstimulation. It is important to remember that a "normal" FSH is not appropriate when the estradiol is markedly elevated and the LH suppressed. Prepubertal girls may present with breast development, vaginal bleeding, and abdominal distension and young boys with premature puberty.

Treatment

Because of the slow growth of microadenomas (see section on Pituitary Incidentalomas), small nonfunctional or gonadotropin-secreting lesions can be treated conservatively and followed with serial imaging. Adenoma enlargement with mass effect symptoms is an indication for more aggressive management with surgery and or irradiation. However, if the tumor presents as a macroadenoma as it often does, more aggressive treatment can be considered earlier. The use of dopamine receptor agonists and SSAs is helpful in shrinking or at least preventing further growth of some of these tumors and can be used in conjunction with surgery and irradiation [31].

Prolactin Excess

Hyperprolactinemia is described in a subsequent section of this chapter

Pituitary Incidentalomas

Pituitary adenomas detected as incidental findings on head MRI or CT scans are called pituitary incidentalomas. Patients with pituitary incidentalomas should be screened for hypersecretion of prolactin (PRL), acromegaly (IGF-1), CD (salivary and urine cortisol levels), and TSH, and those with macroadenomas should also be screened for hypopituitarism and for visual field defects if the tumor abuts the optic chiasm. Growth of nonfunctioning pituitary adenomas without treatment occurs in about 10% of microadenomas and 24% of macroadenomas over 10 years. In the absence of hypersecretion, hypopituitarism, or visual field defects, patients may be followed up by periodic screening by MRI. Growth of a pituitary incidentaloma is an indication for surgery.

IMAGING OF THE HYPOTHALAMIC–PITUITARY SYSTEM

Radiologic Imaging Techniques

MRI specifically focused on the sellar region is the imaging modality of choice for visualization of hypothalamic–pituitary anatomy. Standard protocol consists of 2 to 3 mm sections of sagittal and coronal T1- and T2-weighted images with and without contrast enhancement. This technique delineates the pituitary gland, stalk, optic tracts, and surrounding structures such as the cavernous sinus. The more widely spaced cuts of a routine brain MRI are often inadequate to visualize small pituitary tumors. The anterior pituitary is isodense with white matter, and the posterior pituitary exhibits a bright spot of high signal intensity thought to reflect the presence of vasopressin localized within neurosecretory vesicles. Lack of this feature can represent a nonspecific indicator of central diabetes insipidus (CDI). The size of the pituitary gland varies with age and sex. On average, it measures between 3 and 8 mm in height but is generally larger in females than males. The pituitary gland can transiently enlarge during puberty, pregnancy, and in the postpartum period. The stalk should not exceed 4 mm in diameter; a thickened stalk can indicate hypophysitis, histiocytosis, lymphoma, or granulomatous disease [32,33].

Most microadenomas (tumors ≤10 mm) are hypointense on T1-weighted magnetic resonance (MR) images in relation to adjacent pituitary tissue. This difference is accentuated after contrast enhancement with gadolinium (Fig. 1a). Microadenomas can cause gland asymmetry or stalk displacement. Macroadenomas (>10 mm), which tend to be more vascular tumors, show intermediate signal on unenhanced T1-weighted images and can enhance after gadolinium administration. They often enlarge the sella turcica by gradual remodeling of the bony fossa and show frequent extrasellar extension [32]. The normal pituitary gland can be displaced superiorly, although in 40% of cases, the pituitary gland may not be detectable [34]. These tumors can also grow upward toward the optic chiasm and cause draping of the nerves over the tumor, which is often accompanied by visual field abnormalities (Fig. 1b). Subacute hemorrhage may occur, demonstrating high signal on T1- and T2-weighted images due to the presence of hemoglobin degradation products.

CT is superior to MRI in demonstrating cortical bone, often critical in the case of pituitary adenomas causing erosion of the sellar floor and clinoid bones. CT can also identify intralesional calcifications characteristic of craniopharyngiomas, meningiomas, and chordomas [35].

The radiolabeled SSA ^{111}In-pentetreotide may be used to detect the presence of tissues expressing somatostatin receptors [35]. Octreotide scanning may be used to detect both pituitary and ectopic neuroendocrine tumors expressing these somatostatin receptors. It provides both a visual image and a physiologic measure, and increased uptake may predict the response of medical therapy with SSAs. However, given that these receptors are expressed by normal endocrine tissue as well as nonfunctioning adenomas, the specificity of this procedure is limited. It can be helpful when coupled with an abnormal CT or MRI result to confirm diagnosis.

Positron emission tomography (PET) has an evolving role in the evaluation of sellar masses. The use of ^{18}F-fluoroethyl-spiperone (FESP) PET has shown to be specific for differentiating adenomas from other sellar tumors such as craniopharyngiomas and meningiomas [36]. The uptake of FESP is also consistently higher in nonfunctioning adenomas [36]. Currently, the use of PET imaging in the assessment of pituitary tumors is at the research level.

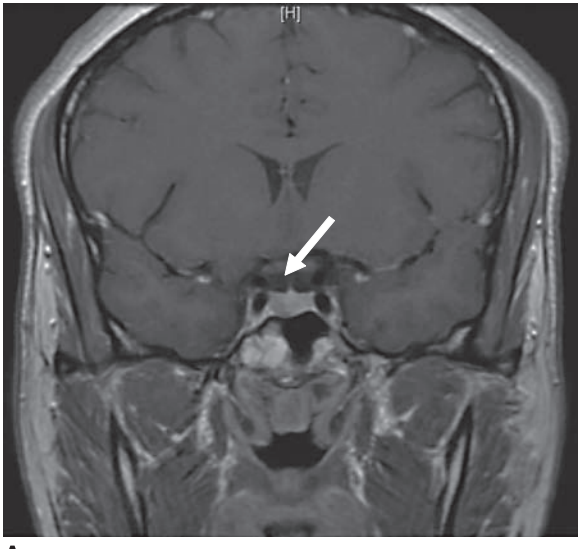

Figure 1a. Coronal T1-weighted MR image through pituitary fossa showing a pituitary microadenoma with hypo-enhancement of the right pituitary gland (*arrow*).

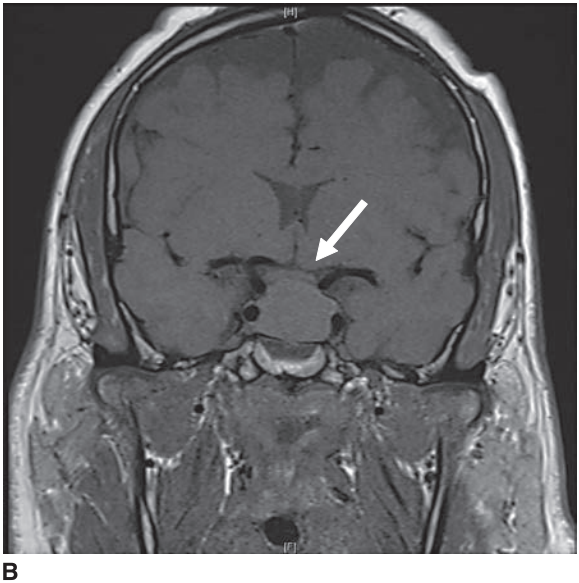

Figure 1b. Coronal T1-weighted MR image through pituitary fossa showing a pituitary microadenoma elevating and compressing optic chiasm (*arrow*).

Other Sellar Lesions

Certain pituitary lesions have specific signal characteristics, which may aid in diagnosis. Rathke cleft cysts and craniopharyngiomas have a common origin from remnants of the Rathke pouch. Craniopharyngiomas are benign yet aggressive squamous epithelial tumors that are predominantly suprasellar. Prominent cystic portions with wall enhancement or varying signal intensities of mixed cystic and solid components with calcification are typical imaging features [32]. CT aids in identification of calcifications, which represent the hallmark of craniopharyngiomas. Rathke cleft cysts are benign lesions containing mucoid material and usually show a sellar epicenter, smooth contour, and reduced MR signal intensity on T1- and increased on T2-weighted imaging [34].

Meningiomas, primitive germ cell tumors, chordomas, and metastases also represent neoplasms, which appear in the sellar region. Meningiomas may arise from any dural site. Characteristic features include dense homogenous enhancement after gadolinium, dural tail enhancement, and adjacent hyperostosis (bone thickening) [34]. Germinomas are generally isointense on T1- and T2-weighted imaging. Chordomas, arising from the notochordal remnants of the clivus, typically produce bony destruction and can lead to cranial neuropathy and neurologic symptoms. Pituitary metastases are found in 1% to 2% of patients, with breast and lung carcinoma being the most common primary sources. Interestingly, the posterior pituitary can be involved in 70% of these cases, and patients may present with DI. The MRI/CT features are those of an enhancing mass, but potential multiplicity of lesions, with a history of a known primary tumor, often leads to the diagnosis.

DISORDERS OF THE PROLACTIN SYSTEM

Pathophysiology

PRL synthesis and secretion by pituitary lactotroph cells is tonically suppressed by hypothalamic dopamine, which reaches the lactotrophs through the portal venous system. PRL acts to induce and maintain lactation in the primed breast. Factors stimulating PRL synthesis and secretion include estrogen, TRH, epidermal growth factor, and dopamine receptor antagonists. Hyperprolactinemia is the most common neuroendocrine condition in clinical practice. Lactotroph adenomas account for approximately 40% of all pituitary adenomas, with 90% being microadenomas [37]. Hyperprolactinemia may also develop due to either impairment of the hypothalamic production of dopamine or compression of the pituitary stalk that impairs dopamine transport to the pituitary. Medications that cause elevated PRL levels include antidepressants and antipsychotics, as well as some antihypertensive agents, opiates, and H2-receptor blockers [38]. PRL levels can also be increased in patients with chronic renal insufficiency or hepatic failure, usually due to reduced clearance. The many etiologies of hyperprolactinemia are listed in Table 1.2.

Clinical Features

Chronic hyperprolactinemia inhibits the pulsatile secretion of GnRH, which leads to a reduction of LH and FSH and a subsequent decline in gonadal hormone production. This leads to amenorrhea/oligomenorrhea, galactorrhea, and anovulatory infertility in premenopausal women. In men, impotence, decreased libido, gynecomastia, and infertility are seen. It can also lead to decreased bone mineral density in both genders [39]. In cases of prolactinomas, mass effect such as headache, visual field defects, decreased visual acuity, and ophthalmoplegia can also be presenting symptoms. Postmenopausal women are often only recognized when a large adenoma causes mass effect.

Table 1.2. Causes of Hyperprolactinemia

PHYSIOLOGIC	**DRUGS**
Pregnancy	Neuroleptics/antipsychotics (e.g., risperidone)
Lactation	Dopamine receptor blockers (e.g., metoclopramide)
Exercise	Antidepressants (e.g., imipramine)
PATHOLOGIC	Antihypertensives (e.g., α-methyldopa)
Hypothalamic–pituitary disorders	Estrogens
Tumors	Opiates
Craniopharyngioma	**NEUROGENIC**
Glioma	Spinal cord lesions
Hamartoma	Chest wall lesions
Microadenoma	Breast stimulation
Macroadenoma	**MISCELLANEOUS**
Metastatic cancer	Primary hypothyroidism
Germinoma	Chronic renal failure
Meningioma	Cirrhosis
Infiltrative disorders	Stress (physical, psychological)
Sarcoidosis	
Giant cell granuloma	
Eosinophilic granuloma	
Lymphocytic hypophysitis	
Others	
Cranial radiation	
Pseudotumor cerebri	
Pituitary stalk section (trauma)	
Empty sella	

Evaluation

If an elevated serum PRL level is detected, pregnancy, the use of medications that raise PRL, and primary hypothyroidism must be ruled out. In addition, renal and hepatic function should be assessed. Once secondary causes have been evaluated, an MRI of the sellar region should be performed. If the patient is taking a medication known to cause hyperprolactinemia, it is still essential to rule out a coincident prolactinoma. This is achieved if the PRL level normalizes after stopping the medication or switching to another one that does not cause hyperprolactinemia. Discontinuation or substitution of an antipsychotic drug should only be performed in conjunction with the prescribing physician. If the drug cannot be discontinued or the onset of hyperprolactinemia does not coincide with the start of treatment, imaging of the pituitary is indicated to confirm etiology [40].

In general, serum PRL levels parallel tumor size. Most patients with PRL levels greater than 150 μg/l will have a prolactinoma [38]. When one encounters a patient with a pituitary macroadenoma associated with only a mild elevation in PRL level, one should suspect either a non-PRL-producing tumor causing

hyperprolactinemia through pituitary stalk compression or an assay artifact known as the hook effect. The hook effect may be observed when extremely high serum PRL concentrations saturate antibodies in the two-site immunoradiometric assay, leading to an artifactually low result. This artifact can be avoided by a 1:100 dilution of the serum [41]. In addition, there are larger PRL forms known as macroprolactin, which are comprised of covalently bound PRL dimers/polymers or complexes of PRL and an anti-PRL IgG antibody. Macroprolactin has reduced biologic activity, but can be detected by some automated PRL immunoassay systems, thus leading to pseudohyperprolactinemia. It is estimated to account for approximately 10% of hyperprolactinemia [42]. Macroprolactinemia does not tend to cause symptoms and signs of hyperprolactinemia. Its clinical relevance is mainly in avoiding expensive workup of hyperprolactinemia and a delay in the diagnosis by inappropriately relating patient symptoms to the macroprolactinemia [43].

Management

Dopamine agonists (DA) are the first line of management in patients with hyperprolactinoma. Dopamine is the endogenous negative regulator of PRL release, PRL gene expression, and lactotroph proliferation; thus, medical treatments are based on activation of the lactotroph D2 receptor [38]. All patients with macroadenomas and symptomatic patients with microadenomas require treatment. The goals of therapy are reduction of tumor size, if the cause is a prolactinoma, and the correction of the hyperprolactinemia to treat the gonadal dysfunction and galactorrhea. Patients with mild hyperprolactinemia with regular menses who wish to become pregnant may also require treatment [39]. However, asymptomatic patients with microprolactinoma or idiopathic hyperprolactinemia often do not require treatment. Hypogonadal women with microadenoma who are not interested in pregnancy may be treated with oral contraceptives as microadenomas do not progressively increase in size in 90% to 95% of cases [44]. Such patients should be carefully monitored with periodic PRL measurements and occasional MRI to assess tumor size.

Dopamine receptor agonists normalize PRL and decrease the size of the tumor in a significant number of patients. DA include bromocriptine and cabergoline (ergot derivatives) and quinagolide (nonergot derivative) available outside the United States. Pergolide was withdrawn from the US market in 2007 following concerns of cardiac valvular damage [38]. Cabergoline, with a high affinity for the lactotroph D2 receptor, is often considered the initial DA of choice, although it is more expensive. In a randomized trial involving 459 women, cabergoline was associated with fewer side effects and normalized PRL levels in 83% of patients compared to 59% of those treated with bromocriptine [45]. Visual field abnormalities normalized in 70% of patients, and tumor shrinkage was seen in 67% of cases [46]. Visual field improvement may often occur within weeks. In addition, cabergoline may be effective in patients intolerant or resistant to bromocriptine [46]. Adverse effects include gastrointestinal (GI) symptoms and orthostatic hypotension, which can be minimized by slow titration of medication dosage. Cabergoline is started at a dose of 0.25 mg once or twice weekly and titrated up to achieve a normal PRL level. Repeat imaging of the pituitary is usually done in 6 months to determine response to therapy. Bromocriptine may be used if cost of treatment is an issue.

Studies [47,48] have suggested that the high doses of cabergoline used to treat Parkinson patients may be associated with cardiac valve insufficiency. The cumulative dose was greater than 3 mg/d, significantly higher than that routinely administered to prolactinoma patients (0.25–3 mg/wk). The majority

of recent studies evaluating cardiac valves in patients receiving standard doses of cabergoline for hyperprolactinemia have found no clinically significant increase in valvulopathy [49–51].

DA withdrawal may be considered in select patients with at least 2 years of therapy demonstrating normalization of serum PRL and no evidence of persistent tumor on MRI. However, careful continued monitoring with PRL levels and pituitary imaging is required. The risk of recurrence after withdrawal ranges from 26% to 69%, with recurrence predicted by PRL levels at diagnosis and tumor size [37,52,53]. Discontinuation of treatment is not recommended for patients with macroadenomas exhibiting extrasellar involvement or persistent hyperprolactinemia.

Transsphenoidal surgery is indicated in patients with pituitary apoplexy, persistent visual field deficits, or increasing tumor size despite an optimal trial of medication. It should also be considered in symptomatic patients intolerant of dopamine agonist therapy. Patients with DA agonist–resistant prolactinomas by definition have more aggressive tumors; thus, recurrence rates after surgery tend to be higher. For patients who fail surgical treatment, radiation therapy may be given.

In the case of medication-induced hyperprolactinemia, if stopping the medication is not possible, then treatment is usually with sex steroid replacement to treat the hypogonadism or rarely with a DA. Giving a DA to psychiatric patients who have medication-induced hyperprolactinemia must be carefully considered as it may worsen the underlying psychiatric condition [54].

Pregnancy and Hyperprolactinemia

DA are used to restore normal menses and treat PRL-induced infertility in women but are discontinued shortly after pregnancy is diagnosed to limit fetal exposure. The high estrogen levels of pregnancy can stimulate lactotroph cell hyperplasia as well as PRL synthesis and secretion; thus, prolactinomas may enlarge during pregnancy. In pregnant women with prolactinomas who have not been treated by surgery or radiation, 2.2% of microadenomas and 27.9% of macroadenomas will have clinically significant growth during pregnancy [54,55]. Surgical debulking of a macroadenoma with suprasellar extension before pregnancy to prevent growth during pregnancy is debatable and should be individualized and discussed with each patient. Patients with macroadenomas should have serial visual field assessments during pregnancy and an MRI only if clinical evidence for tumor growth. PRL levels, which normally increase during pregnancy, can be variable in the setting of prolactinomas and often do not accurately reflect tumor status; thus, PRL measurements are not recommended during pregnancy. If symptomatic tumor enlargement occurs, reinstitution of DA therapy is preferred to surgery. However, surgery or delivery if the fetus is near term should be performed if there is no response to medical treatment and vision loss is progressive. If necessary, both bromocriptine and cabergoline [56,57] have been reported safe in pregnancy, but bromocriptine is preferred as it has the largest safety database with assessment in over 6,000 pregnancies [55]. Breastfeeding has not been shown to increase the risk of lactotroph adenoma growth and can be safety instituted in women who do not require DA therapy.

ACROMEGALY

Definition

Prolonged excessive secretion of GH results in acromegaly. GH causes hepatic production of IGF-1, which over the years leads to overgrowth of bone, soft tissues, and internal organs, and thus contributes to left ventricular hypertrophy,

cardiomyopathy, sleep apnea, and diabetes mellitus. Pituitary gigantism occurs when GH excess begins before epiphyseal fusion in childhood.

Etiology

Pituitary somatotroph adenomas secreting GH cause 98% of cases of acromegaly. Most of these adenomas secrete exclusively GH, with 25% to 30% secreting both GH and PRL. Ectopic GH secreted by neoplasms of the pancreatic islet cells and lymphoma account for fewer than 1% of cases. Rarely, excess GHRH (growth hormone–releasing hormone) from hypothalamic tumors including ganglioneuromas and peripheral neuroendocrine tumors cause acromegaly [58].

Epidemiology

The incidence of acromegaly is approximately three to four per million population. The disease is most commonly diagnosed in the fifth decade. Because of gradual onset of symptoms, GH excess has usually been present for 7 to 10 years before diagnosis.

Pathophysiology and Clinical Presentation

Prolonged excesses of GH and IGF-1 cause acral changes including enlarged hands and feet and coarsened facial features. Joint cartilages and synovial tissues hypertrophy, leading to arthritis and arthralgias.

Cardiac function is frequently impaired, first seen as left ventricular hypertrophy with diastolic dysfunction and dysrhythmias. Systemic hypertension magnifies the cardiac dysfunction. Obstructive and central sleep apnea occur in more than 50% of patients. GH excess contributes to insulin resistance, with glucose intolerance and diabetes commonly seen.

Over 65% of GH-secreting pituitary lesions are macroadenomas. These tumors can present with mass effects such as headache, impaired peripheral vision, and cranial nerve palsies. Patients can also have loss of other pituitary trophic hormones such as FSH, LH, TSH, and ACTH.

Diagnosis

The major diagnostic criteria for acromegaly are elevation of IGF-1 and nonsuppressibility of GH in response to oral glucose loads. Random GH levels are often misleading because of the pulsatile nature of GH secretion and its short plasma half-life (~20 minutes). Patients with acromegaly have pulses of GH secretion, which are of greater magnitude and can lead to tonically elevated GH levels.

IGF-1, 80% of which is produced by the liver, reflects GH secretion during the past day. IGF-1 is responsible for most of GH's growth-stimulating effects and is a stable, integrated assessment of GH activity [59]. IGF-1 levels vary with age and gender and are elevated in essentially all patients with acromegaly. IGF-1 ranges are highest in teenagers and lowest in adults older than 60 years. IGF-1 is lowered by systemic illnesses including malnutrition, renal failure, and liver failure. If IGF-1 is not elevated, active acromegaly is not present, and no further diagnostic testing is required.

In patients with elevated IGF-1, GH response to oral glucose tolerance testing is assessed. Unaffected patients will have GH levels less than 1 mg/ml on standard radioimmunoassays and less than 0.4 ng/ml on ultrasensitive assays 2 hours after a 75-g oral glucose load.

MRI of the pituitary is obtained after GH hypersecretion has been documented. If the MRI does not reveal a focal lesion or diffuse pituitary hyperplasia is suspected, rare syndromes of ectopic GH- or GHRH-secreting lesions should be considered. GHRH levels should then be obtained. Chest and abdominal imaging assist in localizing ectopic sources of GH production listed above.

Treatment

The therapy for acromegaly now commonly involves a combination of transsphenoidal surgery, pharmacologic agents, and radiotherapy [60]. The goals of therapy for acromegaly include normalization of age- and gender-adjusted IGF-1, GH less than 0.4 ng/ml (ultrasensitive assay) after glucose load, and alleviation of mass effect [61]. The correction of GH excess will reduce clinical signs and may also improve cardiac function, sleep disorders, and glucose intolerance. If untreated, mortality accelerates largely from cardiovascular disease. Effective treatment leading to prolonged normalization of GH and IGF-1 can reduce these mortality rates [60].

Neurosurgery

Given that the likelihood of postoperative normalization of IGF-1 and GH in large invasive macroadenomas is generally 50% or less, medical therapy remains the primary approach in large lesions. Transsphenoidal resection is the treatment of choice for microadenomas and macroadenomas confined to the sella and without bony invasion, as well as for macroadenomas that are causing visual disturbances.

Surgical cure rates of approximately 70% to 90% are seen in appropriately selected microadenomas, yet more than 65% of acromegaly cases present as macroadenomas with postoperative cure rates closer to 50% [62–65]. However, criteria for cure and duration of follow-up have varied, which makes comparison of studies difficult. Current criteria for controlled disease are listed earlier in this section [61].Cure rates have increased over time as imaging and surgical techniques have improved, with better outcomes being seen by surgeons and centers with higher case volumes. The United Kingdom National Acromegaly Study Group found that target levels of GH and IGF-1 at 1 year postsurgery were more readily achieved in cases treated after 2000 when a smaller number of surgeons performed more of the cases [66].

Somatostatin Analogs

Somatostatin, or somatotropin release–inhibiting factor, is the physiologic inhibitor of GH. Octreotide Long -Acting Release formulation (LAR) and lanreotide Autogel (ATG) are synthetic analogs of somatostatin that are available as monthly depot preparations. These SSAs bind to the somatostatin receptor subtypes 2 and 5 and decrease GH secretion [67]. Both agents have similar efficacy in lowering IGF-1 and GH [68]. The lanreotide ATG is given by a deep subcutaneous injection, while octreotide requires larger-volume IM injections. These agents are most commonly used in patients who do not achieve normal IGF-1 and GH levels postoperatively. Primary octreotide therapy should be considered in patients in whom surgical cure is unlikely [69]. The depot octreotide preparation has been shown to normalize IGF-1 in 73% and GH in 69%, whether given as primary therapy or as postoperative adjunctive therapy [70]. Preoperative octreotide can decrease tumor size and improve clinical symptoms and cardiopulmonary function before surgery. A systematic literature review of tumor shrinkage with SSAs revealed that 36.6% of treated patients showed a significant decrease in tumor volume, averaging 19.4% [71]. Results of clinical studies with preoperative octreotide have not shown consistent improvement in surgical outcomes [72,73]. Because microadenomas can have 90% cure rates with expert neurosurgeons, it may be difficult to show further improvement with preoperative SSAs. Preoperative therapy controlling IGF-1 and GH may improve cure rates in macroadenomas, in which general cure rates are approximately 50% [74]. The Preoperative Octreotide Treatment of Acromegaly (POTA) trial revealed increased cure rates based on IGF-1 levels at 3 months postsurgery in patients with

macroadenomas who received 6 months of preoperative octreotide. No improvement in cure rates was seen with the preoperative octreotide in microadenomas in this study [75]. Postulated reasons for the improvement with preoperative SSAs include decreased adenoma size and medication-induced changes in tumor consistency, allowing better discrimination between tumor and normal pituitary tissue.

Radiation Therapy

External beam fractionated radiation therapy, delivered over 20 to 25 sessions, controls tumor growth, but it is not likely to achieve normalization of IGF-1 or GH. Levels of these hormones decline gradually after at least 10 years [76]. Loss of pituitary trophic hormones is a late consequence of radiation therapy. Radiation-induced neoplasms and cerebrovascular accidents, while uncommon, can also occur more often as consequences of this fractionated therapy as compared to stereotactic radiosurgery. Stereotactic radiosurgery (e.g., gamma knife, proton beam, and LINAC-based radiosurgery) delivers focused high-dose therapy in one or several treatment sessions and can lower IGF-1 and GH more rapidly with less chance of hypopituitarism [9,77]. A study of proton beam stereotactic surgery in patients with persistent acromegaly postsurgery revealed 59% achieved normal IGF-1 after a median of 6.3 years. New hormone defects were noted in 38% in this study [78]. Large lesions and those close to the optic chiasm are better treated with fractionated external beam radiation therapy. SSAs should be held for at least 3 months before radiation procedures to allow washout of the suppressive effect of these analogs to allow for maximal uptake of radiation into the lesions.

Dopamine Agonists

Cabergoline and bromocriptine uncommonly normalize IGF-1 or GH levels when used as primary therapy [79,80]. These oral agents have been used as additive therapy when surgery, radiation, and SSAs do not normalize hormone levels. Cabergoline, the more effective agonist, is more likely to lower IGF-1 and GH in somatotroph adenomas cosecreting PRL. Cardiac valvular abnormalities have been seen with high doses of cabergoline used in Parkinson disease [47,48]. While the cabergoline doses used to treat elevated GH are lower than those used in Parkinson, consider echocardiography if high cabergoline doses are employed.

Growth Hormone Receptor Antagonist

Pegvisomant is a genetically engineered analog of GH that binds to the GH receptor and prevents dimerization of the GH receptor and thusly decreases production of IGF-1. Pegvisomant normalizes IGF-1 in more than 89% of cases [81,82]. GH levels increase with this agent and usually plateau after several weeks. While adenoma growth on pegvisomant is uncommon, tumor size should be monitored [83]. Liver function monitoring is required as significant elevations can occur in 5% of treated subjects [84]. The agent is given by daily subcutaneous injection in patients uncontrolled by or intolerant to SSAs and DA.

DIABETES INSIPIDUS

Definition

DI produces hypotonic polyuria; the cause of this is either deficient secretion of AVP—CDI—or resistance to the action of this hormone—nephrogenic diabetes insipidus (NDI). Primary polydipsia results from inhibition of AVP release due to excess fluid intake.

Etiology

Central Diabetes Insipidus

Most cases of CDI fall into one of three categories: head trauma [85] or neurosurgery, primary or metastatic pituitary neoplasms or granulomatous diseases (e.g., sarcoidosis, histiocytosis X), or idiopathic, which may be related to autoimmune destruction of AVP-producing hypothalamic nuclei [86]. Less common etiologies include mutations of genes involved in the production of AVP, infections of the central nervous system (CNS), hypoxic encephalopathy, DIDMOAD (CDI, diabetes mellitus, optic atrophy, and deafness) syndrome, or CNS vascular accidents (e.g., Sheehan syndrome).

Nephrogenic Diabetes Insipidus

Hereditary NDI is caused by X-linked transmission of a deficient V2 receptor for AVP and also an autosomal dominant defect in the aquaporin-2 gene [87]. Many drugs, including lithium, antibiotics (e.g., demeclocycline), antivirals, antifungals, and antineoplastics, can cause acquired NDI, which usually resolves with discontinuation of the agent; however, long-term lithium therapy tends to cause irreversible NDI [88]. Vasopressin V2 receptor antagonists conivaptan and tolvaptan treat hyponatremia by causing NDI. Persistent hypercalcemia (>11 mg/dl) and severe hypokalemia (<3 mEq/l) can also cause resistance to the action of AVP, with this form of NDI resolving with correction of the electrolyte abnormalities.

Gestational DI is an unusual polyuric condition caused by increased placental vasopressinase activity, which resolves postpartum [88]. This form of DI responds well to DDAVP since this agent is resistant to vasopressinase.

Pathophysiology

AVP is produced in the supraoptic and paraventricular nuclei of the hypothalamus. The hormone travels down the pituitary stalk for storage in the posterior pituitary. AVP decreases urine flow by increasing reabsorption of solute free water in the distal and collecting tubules of the kidney. AVP binds to the tubular V2 receptors, leading to production of cyclic adenosine monophosphate, which increases tubular permeability to water by perforating the luminal surface with water channels made of aquaporin-2 [89,90].

Hypothalamic osmoreceptors and baroreceptors in the carotids, the atria, and the aorta regulate the secretion of AVP.

Diagnosis

Urine volume exceeding 3 l or 50 ml/kg/d with 24-hour urine osmolality of 300 mOsm or less suggests DI. One must rule out uncontrolled diabetes mellitus; however, this condition usually has a higher urine osmolality owing to glycosuria.

The clinical history helps distinguish among CDI, NDI, and primary polydipsia. Trauma or pituitary neoplasm increases the suspicion for CDI, whereas a family history or onset in childhood suggests NDI. One commonly sees a history of psychiatric disturbances in association with primary polydipsia. Thirst can be affected directly by the psychiatric problems or by the medications used in treatment. The serum sodium is normal or slightly elevated in CDI and NDI, so long as thirst is intact and water is available. In primary polydipsia, sodium may be low as a result of water overload.

Water-deprivation testing may be required to differentiate these conditions. Water is withheld, and the patient's weight, blood sodium, and urine and plasma osmolalities are closely monitored. The patient is given exogenous AVP once urine osmolalities have been stable (<10% variability) for several determinations

or the serum sodium is greater than 146 mmol/l. After the patient has achieved a plasma osmolality that exceeds 295 mOsm, exogenous AVP does not further increase urine osmolality in unaffected patients. Normal patients and patients with primary polydipsia have increases in urine osmolality less than 10%. In CDI, urine osmolality increases exceed 50%. With partial AVP deficiency, patients show a lesser increase. In patients with urine osmolality increases between 10% and 50%, plasma AVP levels may be helpful with elevated levels supporting NDI and low levels suggesting CDI. Patients with NDI do not increase urine osmolality above plasma osmolality in response to AVP.

Pituitary imaging in DI is discussed in the earlier section on imaging of the hypothalamic–pituitary axis.

Treatment

Central Diabetes Insipidus

DDAVP is a synthetic modification of AVP that has prolonged antidiuretic activity without vasopressive effects. DDAVP is available by injection form, nasal spray, and tablets. Nasal DDAVP spray has approximately 10% potency of the parenteral form. Due to poor GI absorption, DDAVP tablets have approximately 10% the potency of the nasal spray. The usual starting dose of DDAVP is 0.1 mg orally or one 10-μg spray once or twice daily. The medication is titrated based on clinical symptoms, urinary specific gravity measurements, and blood sodium levels. The patient can become hyponatremic from water intoxication with DDAVP, so dosage must be periodically reassessed, and patients may need to limit their usually liberal fluid intake when treatment is initiated. DDAVP intravenously or subcutaneously is commonly used in the postoperative period after pituitary surgery when patients are unable to use the oral or intranasal routes.

Other agents that increase AVP secretion (e.g., clofibrate) or action (e.g., chlorpropamide, indapamide, carbamazepine) are less effective, and their use is limited.

Nephrogenic Diabetes Insipidus

DDAVP, even in supraphysiologic doses, has a limited response in hereditary NDI because this condition is caused by resistance to AVP. In acquired NDI, treatment of metabolic and pharmacologic causes can decrease urinary volume and usually lead to resolution of this form of NDI. Thiazide diuretics may decrease urine volume by causing mild volume depletion. In conjunction with a low-salt diet, thiazides increase proximal tubular absorption of sodium and water, leading to decreased water delivery to the collecting tubule where AVP action occurs. Nonsteroidal anti-inflammatory drugs decrease renal prostaglandins and thus augment AVP action, decreasing urine volume in NDI.

CUSHING DISEASE

Etiology and Pathogenesis

Cushing syndrome (CS) is a hormonal disorder that occurs when the body's tissues are exposed to excessive levels of cortisol for a long period of time. Cortisol is produced by the adrenal glands and helps the body respond to stresses, such as surgery and illness, and recover from infections. Cortisol also helps maintain blood pressure and cardiovascular function and regulates the metabolism of proteins, carbohydrates, and fats.

CS due to increased pituitary ACTH secretion by a pituitary tumor is called CD. The most common cause of CD is a benign pituitary microadenoma [91]. Excessive

ACTH secretion can also result from ectopic ACTH secretion (EAS) from small cell lung cancer and atypical carcinoids of the bronchus, thymus, gut, or ovary. All other less common etiologies leading to CS are discussed in Chapter 3.

Clinical Manifestations

Symptoms and signs reviewed in Chapter 3. The onset of symptoms is usually insidious and gradual over 2 to 10 years before diagnosis. An important difference between CD and adrenal causes of CS is hyperpigmentation (palmar creases and pressure points), which is seen in CD. It is due to melanocyte-stimulating hormone production as a byproduct of ACTH synthesis from POMC.

Laboratory Findings

After establishing the diagnosis of CS as detailed in Chapter 3, the next step is to determine if CS is ACTH dependent. Plasma ACTH below 5 to 10 pg/ml (depending on the assay) at 9 a.m. is indicative of an ACTH-independent etiology, whereas a level above 20 pg/ml is indicative of ACTH dependency. ACTH between 10 and 20 pg/ml is indeterminate but usually indicates an ACTH-dependent etiology [92,93]. When ACTH falls into this indeterminate range, a CRH stimulation test can be helpful with measurement of ACTH. The CRH stimulation test depends on the concept that a pituitary adenoma in CD exhibits more CRH receptors than tumors with EAS. ACTH does not change appreciably in ACTH-independent cases (EAS) in response to CRH. The test is performed by administering ovine or human CRH as an IV injection 1 μg/kg body weight, or a total dose of 100 μg. ACTH and cortisol are measured at baseline and then at 15-minute intervals for 2 hours after the injection. The criteria consistent with CD vary considerably between different studies. One used the rise from baseline in peak plasma ACTH greater than or equal to 105% (sensitivity 70%, specificity 100%) or rise in cortisol greater than or equal to 14% after human CRH injection (sensitivity 85%, specificity 100%) [94].

High-Dose Dexamethasone Suppression Test

After establishing ACTH dependence, the source of ACTH must be determined. The most common test used is the high-dose dexamethasone suppression test (HDDST). High-dose dexamethasone suppresses ACTH in CD but not in EAS. Dexamethasone 2 mg is given every 6 hours for eight doses and 24-hour urinary free cortisol (UFC) and 17-hydroxysteroids are measured before and on the second day. A fall of 24-hour UFC by greater than 90% and of 24-hour urinary 17-hydroxycorticosteroids by greater than 69% identify patients with CD (sensitivity 79%, specificity 100%) [95]. In the overnight HDDST (overnight dexamethasone suppression test [DST]), dexamethasone 8 mg PO is given at 11 p.m. Cortisol level is measured at 8 a.m. on the day dexamethasone is given and at the same time the next morning. A fall of plasma cortisol by greater than 68% indicates CD with a sensitivity of 71% and specificity close to 100% [96]. Limitations of the overnight suppression test include some benign tumors with EAS, which can be suppressed by HDDST, and some pituitary macroadenomas, which may not. The dexamethasone suppression test can produce false-positive results in patients with depression, alcohol abuse, high estrogen levels, acute illness, and stress. Conversely, drugs such as phenytoin and phenobarbital may cause false-negative results in response to dexamethasone suppression. For this reason, patients are advised to stop taking these drugs at least 1 week before the test.

Bilateral Inferior Petrosal Sinus Sampling

Pituitary MRI should be done in all patients with ACTH-dependent CS and will reveal the adenoma in 50% to 70% of cases. A pituitary tumor larger than 6 mm

with biochemical testing indicating CD may be sufficient to confirm the diagnosis. However, 10% of unaffected patients may have pituitary incidentaloma on MRI scans [97]. Therefore, if the results are not diagnostic, bilateral inferior petrosal sinus sampling (BIPSS) should be done. This procedure requires placement of catheters in the left and right inferior petrosal sinuses and measuring ACTH simultaneously from both sinuses and peripherally before and after CRH stimulation. A baseline (before CRH) ratio of petrosal sinus to peripheral vein ACTH of 2.0 or higher and a post–CRH stimulation ratio above 3.0 confirms CD with sensitivities of 95% and 100% respectively and 100% specificity for both. A gradient between right and left petrosal sinus (>1.4) helps in lateralization of the lesion [98]. It is debatable whether the BIPSS should be done routinely since incidentalomas are common. An alternative to the BIPSS is the jugular vein sampling (JVS), which is less invasive and has shown promising results [99].

The most common tumors causing EAS are neuroendocrine tumor and small cell lung cancer. CT and MRI are commonly used to localize the source of EAS. However, in 30% to 50% of patients with EAS, the source of ACTH secretion cannot be found despite repeated imagings over time. The majority of ectopic ACTH-secreting tumors may express somatostatin receptor subtypes. Therefore, the radiolabeled SSA scintigraphy may be useful to localize radiologically unidentified tumors [100]. A lesion of uncertain pathology is more likely to represent a neuroendocrine tumor, and hence an ectopic source of ACTH, if somatostatin scintigraphy is positive. A combination of these studies is frequently recommended to increase the success rate of tumor localization [101].

Unless the tumors are metabolically active, which is usually not the case for EAS, 18-flurodeoxyglucose PET does not generally offer any advantage over conventional CT or MRI [102].

Treatment

The primary therapy of CD is transphenoidal microadenomectomy [103,104]. Initial cure rate is about 86% in microadenoma and 65% in macroadenomas, with worse prognosis in patients with extensive suprasellar extension [103,104]. Those treated with surgery successfully will frequently require glucocorticoids taper for a year or more to avoid relative clinical adrenal insufficiency caused by prolonged exposure to high cortisol levels. One study revealed a long-term cure rate of 67% [105]. When judged by long-term outcome, patients demonstrating cortisol circadian rhythm restoration with serum cortisol at 11 p.m. less than 1.8 μg/dl have the highest long-term remission rates, 85% to 100% [106]. Persistent disease after surgery is associated with increased long-term mortality [104]. All patients should be evaluated annually for recurrence.

When CS cannot be controlled with surgery, conventional external beam or stereotactic radiosurgery can be used to control cortisol levels and tumor growth in many patients. However, it generally takes significantly longer to lower cortisol levels with external beam radiotherapy as compared to stereotactic radiotherapy. Maximum benefit is usually achieved within 3 to 12 months. External beam radiation reliably causes loss of normal pituitary function 5 to 10 years after treatment.

Patients who do not respond to surgery or radiation are treated by medical means [107] (discussed in Chapter 3) or surgical bilateral adrenalectomy. There are several adrenal enzyme inhibitors available to control cortisol levels. These include ketoconazole, aminoglutethimide, and metyrapone, which all inhibit

cortisol production in the adrenal glands. All are relatively effective, but each has side effects and corrects only the cortisol level, not the cause of CS. Treatment of EAS is to remove the underlying tumor. Medical or surgical adrenalectomy is also indicated in patients with incurable or unlocalizable tumors.

SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE SECRETION

The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is a constellation of findings that result from excess water in relation to sodium. It is dilutional, euvolemic hyponatremia.

Etiology

SIADH can arise from several disease states and pharmacotherapies. The main categories are listed in Table 1.3. Those arising from the CNS cause SIADH by increasing antidiuretic hormone (ADH) secretion through the body's physiologic pathway. Carcinomas that are causative usually produce ADH directly, regardless of the hypothalamic–pituitary axis, as part of a paraneoplastic syndrome. Small cell lung carcinoma is the most common oncologic cause of SIADH [90]. In a study by Comis et al., at least 46% of patients with small cell lung cancer had elevated ADH levels [108]. Another cause of SIADH that is becoming increasingly prevalent is AIDS. Up to 25% of hospitalized patients with AIDS have possible SIADH [109]. The fatality rate of patients with hyponatremia (sodium < 130 mEq/l) is 60-fold compared to that of patients without documented hyponatremia, though the mortality is typically related to comorbid conditions rather than the hyponatremia itself.

Epidemiology

The epidemiology of SIADH can be extrapolated from that of hyponatremia. SIADH can occur in anyone with any of the precipitators already suggested, but the elderly, the hospitalized, and residents of chronic care facilities are at greatest risk.

Pathophysiology

SIADH begins when a water imbalance occurs, and the body receives more water than it excretes. ADH is produced by supraoptic and paraventricular nuclei in the hypothalamus and transmitted via the neuronal axons to the posterior pituitary where it is secreted [110]. It is released when a decrease in the effective circulatory volume is sensed by vascular baroreceptors primarily located in the large arterial vessels. The key action of ADH in the kidney is to trigger the insertion of aquaporin-2 into the principal cells of the collecting duct. Aquaporin's selective permeability allows water reabsorption and consequently urine concentration. If excess ADH is present, the patient is unable to excrete the additional amount of water due to excessive water reabsorption through aquaporin. The intracellular and extracellular fluid volumes increase subsequently, and the concentration of sodium decreases, leading to hyponatremia. This elevated level of fluid is detected by the renal juxtaglomerular cells, and the level of renin and aldosterone decrease. Depressed levels of renin and aldosterone promote sodium excretion, which prevents fluid overload but also perpetuates the low sodium concentration.

Diagnosis

Clinical Findings

Not all patients with SIADH are symptomatic. The likelihood of becoming symptomatic depends on the rate at which sodium concentration is changed rather

Table 1.3. Causes of Syndrome of Inappropriate Secretion of Antidiuretic Hormone

Central nervous system
Stroke (hemorrhagic or ischemic)
Hemorrhage
Neoplasm
Infection
Hydrocephalus
After transsphenoidal hypophysectomy
Schizophrenia
Lupus
Acute intermittent porphyria
Carcinoma
Small cell lung carcinoma
Pharyngeal carcinoma, thymoma
Pancreatic carcinoma
Bladder carcinoma
Lymphoma, sarcoma
Others: prostate, duodenal, ovarian, mesothelioma
Pulmonary
Infections (pneumonia, abscess, tuberculosis)
Bronchiectasis
Mechanical ventilation
Medication related
Psychiatric: antipsychotics, tricyclics, selective serotonin receptor inhibitors, carbamazepine
Neurologic: narcotics, ecstasy
ACE inhibitors
Oncologic: vincristine, vinblastine, cyclophosphamide
Endocrine: oxytocin, DDAVP, chlorpropamide, clofibrate
Infections
CNS and pulmonary infections, as above
Acquired immunodeficiency syndrome
Idiopathic

than in the absolute amount of change. Presentations range from mild constitutional symptoms (e.g., fatigue, anorexia, nausea, mild headache) to more serious signs (e.g., seizures, coma, and death). Generally, symptoms develop when the sodium concentration falls below 125 mmol/l. More serious neurologic signs, such as coma, seizures, decreased reflexes, and altered mental status, appear as the sodium concentration decreases to 115 mmol/l. When the sodium level is below 115 mmol/l, sudden death is a risk.

Laboratory Findings

In the evaluation of hyponatremia and SIADH, key tests are plasma osmolality, urine osmolality, and urine sodium. These tests will reveal a low plasma

osmolality and an elevated urine osmolality. The kidney, as already described, is excreting more sodium, so the urinary sodium level will be high, exceeding 20 mmol/l. Other laboratory values (e.g., hematocrit, blood urea nitrogen, uric acid) are decreased secondary to dilution. Besides these laboratory values, the diagnosis of SIADH requires that the patient have no other causes for hyponatremia, such as congestive heart failure, cirrhosis, renal failure, adrenal insufficiency, thyroid disease, or electrolyte imbalance.

Treatment

Therapy for both acute and chronic hyponatremia includes correction of the underlying cause.

Short-Term Therapy

Treatment depends on the patient's clinical picture. If the patient is mildly symptomatic, one can fluid restrict the patient to 1 l/d. If hyponatremia is severe and patient is symptomatic, fluid restriction alone is not adequate. One needs to add sodium in excess of water, usually in conjunction with furosemide. This can be done with the addition of 3% saline solution. The change in sodium concentration should not exceed 8 to 12 mmol/l in the first 24 hours. The rate should be fast enough to resolve symptoms but not so rapid as to cause complications such as central pontine myelinolysis. One guideline is to infuse 3% saline solution at a rate of no more than 0.5 ml/kg/h to increase the sodium concentration by 1 to 2 mmol/l/h until symptoms resolve or the sodium concentration rises by half of the deficit [90]. The approximate sodium deficit can be estimated by using the following formula (consider 0.5 l/kg for females):

Na^+ deficit (mEq) = (desired Na^+ − measured Na^+) × 0.6 l/kg × weight (kg).

Saline infusion can be stopped when symptoms resolve or when the sodium concentration rises to 125 to 130 mmol/l. Sodium concentration and urine output should be checked every 1 to 2 hours to ensure that the rate of correction is appropriate and to detect whether the syndrome resolves.

Central pontine myelinolysis remains a potential danger of sodium replacement. Alcoholism, malnourishment, and debilitation can place patients at increased risk. Additionally, existence of SIADH for longer than 2 days increases the risk of this complication if the sodium level is corrected too rapidly. A multicenter prospective study by Sterns et al. [109] showed that neurologic complications, including central pontine myelinolysis, occurred in patients with chronic hyponatremia whose sodium concentration was corrected faster than 12 mmol/l over 24 hours or 18 mmol/l over 48 hours.

Long-Term Therapy

Fluid restriction as already mentioned, at times with the use of loop diuretics, is the first line of treatment. However, many patients are unable to comply with fluid restriction. Therefore, many patients require medication. Demeclocycline causes NDI and polyuria, which can correct the excess of water seen in SIADH. The usual dose is 600 to 1,200 mg/d. It may take 1 to 2 weeks to see its effect. A study by Forrest et al. compared demeclocycline with lithium and revealed that demeclocycline is superior to lithium in the treatment of SIADH [111].

Vasopressin Receptor Antagonists

A new class of medications, the "vaptans," act by inhibiting the action of vasopressin on its receptors —V_{1A} (causing vasoconstriction, platelet aggregation, inotropic stimulation, myocardial protein synthesis), V_{1B} (causing secretion of ACTH), and V_2 (causing water reabsorption and release of von Willebrand factor and factor VIII). Blockade of V_2 receptors in the renal collecting ducts

reduces water reabsorption, promoting aquaresis, decreasing urine osmolality, and increasing plasma sodium concentration, which will improve hyponatremia [112].

Conivaptan and tolvaptan currently are the vasopressin receptor antagonists that are FDA-approved for the treatment of euvolemic hyponatremia in hospitalized patients. Conivaptan is an intravenous dual V_{1A}/V_2 antagonist [113,114], and tolvaptan is a selective oral vasopressin V_2 receptor antagonist. Though tolvaptan is an oral agent, it should be initiated and reinitiated in hospital where serum sodium can be monitored closely. Both are indicated for hypervolemic and euvolemic hyponatremia associated with SIADH, congestive heart failure, and liver cirrhosis. A recent study has confirmed the long-term efficacy of tolvaptan in 111 patients over a mean duration of treatment greater than 700 days [115]. Tolvaptan therapy can result in a sustained improvement in serum sodium concentration without an unacceptable increase in adverse events [116]. Both vaptans should be initiated in a closely monitored setting to prevent rapid correction of serum sodium, which can result in central pontine myelinolysis [117].

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    In an attempt to avoid GH stimulation tests, which are invasive, time-consuming, and associated with side effects, the authors determined that adult GHD could be predicted with 95% accuracy, high specificity (89%), and moderate sensitivity (69%) by the presence of three or more PHDs or a serum IGF-I concentration less than 84 μg/l (11 nmol/l) using data from 817 adults with GHD. In clinical practice, it is recommended that other causes of low serum IGF-I be excluded before applying these diagnostic criteria.

26. (1C) **Biller BM,** et al. Sensitivity and specificity of six tests for the diagnosis of adult GH deficiency. J Clin Endocrinol Metab 2002;87(5):2067–2079.

    This study evaluated the relative utility of six different methods of testing for adult GHD currently used in the United States and developed diagnostic cut-points for each of these tests. Thirty-nine patients with adult-onset hypothalamic–pituitary disease and multiple PHDs were studied in comparison with age-, sex-, estrogen status–, and body mass index (BMI)–matched control subjects. A third group of patients with adult-onset hypothalamic–pituitary disease and no more than one additional PHD was also studied. The primary end point was peak serum GH response to five GH stimulation tests administered in random order at five separate visits: ITT, ARG, (L-DOPA), ARG plus L-DOPA, and ARG plus GHRH. Serum IGF-I concentrations were also measured on two occasions. Three diagnostic cut-points were calculated for each test to provide optimal separation of multiple pituitary hormone–deficient and control subjects according to three criteria: (1) to minimize misclassification of control subjects and deficient patients, (2) to provide 95% sensitivity for GHD, and (3) to provide 95% specificity for GHD. The greatest diagnostic accuracy occurred with the ITT and the ARG plus GHRH test, although patients preferred the latter. There was substantial overlap between patients and control subjects for the ARG plus L-DOPA, ARG, and L-DOPA tests. Although serum IGF-I levels provided less diagnostic discrimination than all five GH stimulation tests, a value below 77.2 μg/l was 95% specific for GHD. The authors concluded that the diagnosis of adult GHD can be made without performing an ITT, provided that test-specific cut-points are used. The ARG plus GHRH test represents an excellent alternative to the ITT for the diagnosis of GHD in adults.

27. (2A) **Borson-Chazot F,** et al. Decrease in carotid intima-media thickness after one year growth hormone (GH) treatment in adults with GH deficiency. J Clin Endocrinol Metab 1999;84:1329–1333.

    This was a multicenter open trial involving 22 GH-deficient patients treated with replacement for 2 years. A decrease in carotid artery intima-media thickness was observed in 21 of 22 patients. GH treatment resulted in a moderate decrease in waist circumference and body fat mass. Conventional cardiovascular risk factors were unmodified except for a transient 10% decrease in LDL cholesterol at 6 months. The decrease in intima-media thickness may indicate a reversal in the atherosclerotic process.

28. (2A) **Murray RD,** et al. Dose titration and patient selection increases the efficacy of GH replacement in GHD adults. Clin Endocrinol 1999;50:749–757.

    This trial was an open study of GH replacement in 65 severely GH-deficient patients who had GH initiated with a low dose (0.8 U/d) and titrated by 0.4-U increments to normalize the IGF-1. Following initiation of GH, serum IGF-1 levels increased significantly and lipid levels decreased, whereas other metabolic parameters were largely unchanged. Improvement in quality of life in GH-deficient adults was proportional to the degree of impairment before initiating therapy. The authors concluded that the use of low-dose titration and selection of a population with greater morbidity reduces the occurrence of overreplacement and increases the efficacy of treatment.

29. (4D) **Beck Peccoz P,** et al. TSH-secreting adenomas. Best Pract Res Clin Endocrinol Metab 2009;23:597–606.

    Excellent comprehensive review of TSH-secreting adenomas summarizing the case reports and series available in the literature

30. (4D) **Greenman Y, Stern N.** Non-functioning pituitary adenomas. Best Pract Res Clin Endocrinol Metab 2009;23:625–638

Thorough investigation of nonfunctioning pituitary adenomas focusing on clinical presentation, diagnostic workup, and treatment options

31. (4D) **Sam S, Molitch ME.** The pituitary mass: diagnosis and management. Rev Endocr Metab Disord 2005;6:55–62.

Excellent review of pituitary enlargement, with special emphasis on nonsecreting pituitary adenomas

Imaging of the Hypothalamic–Pituitary System

32. (4) **Morana G,** et al. Pituitary tumors: advances in neuroimaging. Endocr Dev 2010;17:160–174.

Neuroradiologic characteristics of pituitary region tumors are described with an emphasis on pituitary adenomas and their differential diagnosis.

33. (2) **Simmons GE,** et al. MR imaging of the pituitary stalk: size, shape, and enhancement pattern. AJR Am J Roentgenol 1992;159:375–377.

A retrospective study of the MR characteristics of 58 patients defining the size, contour, signal intensity, and enhancement pattern of the normal pituitary stalk

34. (4) **Rennert J, Doerfler A.** Imaging of sellar and parasellar lesions. Clin Neurol Neurosurg 2007;109:111–124.

Overview of relevant MRI and CT characteristics along with clinical findings of pituitary tumors, vascular, inflammatory, and infectious lesions found in the sellar/parasellar region

35. (4) **Melmed S.** Evaluation of pituitary masses. In: DeGroot L, Jameson, J, eds. Endocrinology. 5th ed. Philadelphia, PA: Elsevier Saunders, 2006;387–395.

Comprehensive overview of pituitary gland pathology, parasellar masses, and imaging correlation

36. (4) **Naji M,** et al. Endocrine tumors: the evolving role of positron emission tomography in diagnosis and management. J Endocrinol Invest 2010;33:54–60.

PET imaging, using ^{18}F-fluorodeoxyglucose (FDG) and other radiopharmaceuticals, can be useful in the diagnosis and management of a wide range of endocrine tumors.

Disorders of the Prolactin System

37. (4) **Melmed S,** et al. Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2011;96:273–288.

An evidence-based practice guideline from the Endocrine Society on the diagnosis and management of hyperprolactinemia based on analysis and synthesis of currently available data

38. (4) **Klibanski A.** Clinical practice. Prolactinomas. N Engl J Med 2010;362:1219–1226.

A review of the current clinical practice in the diagnosis and treatment of prolactinomas

39. (4) **Casanueva FF,** et al. Guidelines of the Pituitary Society for the diagnosis and management of prolactinomas. Clin Endocrinol (Oxf) 2006;65:265–273.

A consensus guideline from the Pituitary Society representing recommendations of international experts in the field on the diagnosis and management of prolactinomas based on analysis and synthesis of currently available data

40. (4) **Molitch ME.** Medication-induced hyperprolactinemia. Mayo Clin Proc 2005;80: 1050–1057.

A review encompassing medications that can cause hyperprolactinemia. It includes medications such as antipsychotics, antidepressants, antihypertensives, and drugs that increase bowel motility. The hyperprolactinemia in these cases is commonly symptomatic.

41. (2) **St-Jean E,** et al. High prolactin levels may be missed by immunoradiometric assay in patients with macroprolactinomas. Clin Endocrinol (Oxf) 1996;44:305–309.

A study comparing the clinical and biochemical features of 4 patients with the high-dose PRL hook effect to 54 patients with nonfunctioning pituitary adenomas and 11 patients with macroprolactinomas who underwent surgery from 1989 to 1994. The high-dose hook effect is noted particularly in patients with large tumors; the immunoradiometric PRL assay must be performed with serial dilution.

42. (2) **Vallette-Kasic S,** et al. Macroprolactinemia revisited: a study on 106 patients. J Clin Endocrinol Metab 2002;87:581–588.

One thousand one hundred six consecutive patients investigated for hyperprolactinemia over a 10-year period were analyzed. Among them, 106 patients had macroprolactinemia, a prevalence of about 10%. These 106 patients were prospectively followed and compared to 262 hyperprolactinemic patients without macroprolactinemia.

43. (4) **Gibney J, et** al. Clinical relevance of macroprolactin. Clin Endocrinol (Oxf) 2005;62:633–643.

A review article on the nature, methods of measurement, and bioactivity of macroprolactin. This also covers the epidemiology and natural history of patients with macroprolactinemia.

44. (2) **Schlechte JA,** et al. Long term follow-up of women with surgically treated prolactin-secreting pituitary tumors. J Clin Endocrinol Metab 1986;62:1296–1301.

Fifty-four women with prolactinomas were studied after transsphenoidal surgery. Five years after surgery, 19 women (35%) had normal serum PRL, and 23 (43%) had persistent hyperprolactinemia, while hyperprolactinemia recurred in 12 patients (22%) who had normal PRL levels 6 weeks after surgery. None of the patients with recurrent hyperprolactinemia had radiographic evidence of tumor regrowth.

45. (1) **Webster J,** et al. A comparison of cabergoline and bromocriptine in the treatment of hyperprolactinemic amenorrhea. Cabergoline Comparative Study Group. N Engl J Med 1994;331:904–909.

This randomized, multicenter 24-week trial compared cabergoline with bromocriptine in the treatment of 459 women with hyperprolactinemic amenorrhea. Stable normoprolactinemia was achieved in 83% of women treated with cabergoline and 59% of the women treated with bromocriptine ($p < 0.001$). Adverse effects were noted in 68% of women taking cabergoline and 78% of those taking bromocriptine ($p = 0.03$); 3% required discontinuation of cabergoline, while 12% stopped bromocriptine due to drug intolerance ($p < 0.001$).

46. (2) **Verhelst J,** et al. Cabergoline in the treatment of hyperprolactinemia: a study in 455 patients. J Clin Endocrinol Metab 1999;84:2518–2522.

This large-scale retrospective study of 455 patients with pathologic hyperprolactinemia found that treatment with cabergoline normalized PRL levels in 86% of all patients. Visual field abnormalities normalized in 70% of patients, and tumor shrinkage was seen in 67% of patients. In a subgroup of patients with bromocriptine intolerance, normalization of PRL occurred in 84% of cases; in those with bromocriptine resistance, PRL could be normalized in 70% of cases.

47. (2) **Schade R,** et al. Dopamine agonists and the risk of cardiac valve regurgitation. N Engl J Med 2007;356:29–38.

A case-control analysis of patients with newly diagnosed cardiac valve regurgitation matched with up to 25 control subjects using a national population-based cohort of subjects 40 to 80 years of age who were prescribed antiparkinsonian drugs between 1988 and 2005. The rate of cardiac valve regurgitation was increased with current use of pergolide (incidence rate ratio, 7.1; 95% confidence interval [CI], 2.3 to 22.3) and cabergoline (incidence rate ratio, 4.9; 95% CI, 1.5 to 15.6) but not with current use of other DA.

48. (2) **Zanettini R,** et al. Valvular heart disease and the use of dopamine agonists for Parkinson's disease. N Engl J Med 2007;356:39–46.

Echocardiograms were performed in 155 patients taking DA (pergolide, cabergoline, and nonergot-derived DA) for Parkinson disease and 90 control subjects. Clinically important valvular regurgitation was significantly greater in patients taking pergolide (23.4%) or cabergoline (28.6%) but not in patients taking nonergot-derived DA (0%) as compared with control subjects (5.6%).

49. (3) **Kars M,** et al. Aortic valve calcification and mild tricuspid regurgitation but no clinical heart disease after 8 years of dopamine agonist therapy for prolactinoma. J Clin Endocrinol Metab 2008;93:3348–3356.

A cross-sectional study in which two-dimensional and Doppler echocardiography was performed in 78 consecutive patients with prolactinoma treated with DA for at least 1 year and 78 control subjects. Clinically relevant valvular heart disease was present in 12% of patients versus 17% of controls ($p = 0.141$) and 17% of patients treated with cabergoline versus 3% of patients not treated with DA ($p = 0.062$), thus not achieving clinical significance.

50. (2) **Nachtigall LB,** et al. Gender effects on cardiac valvular function in hyperprolactinaemic patients receiving cabergoline: a retrospective study. Clin Endocrinol (Oxf) 2010;72:53–58.

A retrospective study comparing 100 patients with hyperprolactinemia with controls matched for age, gender, BMI, and hypertension to determine whether there is an association of cabergoline and valvular function according to gender. Overall, cabergoline was not associated with valvulopathy in this cohort.

51. (2) **Vallette S,** et al. Long-term cabergoline therapy is not associated with valvular heart disease in patients with prolactinomas. Pituitary 2009;12:153–157.

A prospective, multicenter study in which a transthoracic echocardiogram was performed in 70 patients with prolactinomas treated with cabergoline for at least 1 year and

70 control subjects matched for age and sex. Moderate valvular regurgitation was found in 5.7% of patients and 7.1% of controls ($p = 0.73$). No patient had severe valvular disease. There was no correlation between the presence of significant valvular regurgitation and cabergoline cumulative dose, duration of treatment, prior use of bromocriptine, age, adenoma size, or PRL levels.

52. (2) **Colao A,** et al. Predictors of remission of hyperprolactinaemia after long-term withdrawal of cabergoline therapy. Clin Endocrinol (Oxf) 2007;67:426–433.

This prospective analysis of a cohort of 221 patients followed up for 24 to 96 months after cabergoline treatment withdrawal demonstrated recurrence of hyperprolactinemia in 25.9%, 33.9%, and 53.1% of patients with nontumoral hyperprolactinemia, microprolactinomas, and macroprolactinomas, respectively. Remission rates were significantly higher in patients achieving PRL levels and maximal tumor diameter at withdrawal below a threshold of 5.4 µg/l and 3.1 mm, respectively.

53. (2) **Dekkers OM,** et al. Recurrence of hyperprolactinemia after withdrawal of dopamine agonists: systematic review and meta-analysis. J Clin Endocrinol Metab 2010;95:43–51.

This meta-analysis of 19 studies including both clinical trials and observational studies involved a total of 743 patients to assess the effect of DA withdrawal in patients with idiopathic hyperprolactinemia and prolactinomas. Withdrawal was associated with persisting normoprolactinemia in 21% of patients. The probability of success was highest when cabergoline was used for at least 2 years.

54. (4) **Molitch ME.** Prolactinomas and pregnancy. Clin Endocrinol (Oxf) 2010;73:147–148.

A commentary on DA use during pregnancy citing a growing body of evidence suggesting both bromocriptine and cabergoline are likely safe during early pregnancy

55. (3) **Bronstein MD.** Prolactinomas and pregnancy. Pituitary 2005;8:31–38.

This observational study and review followed 71 pregnancies in women with microprolactinomas and 51 pregnancies in women with macroprolactinomas. With microprolactinomas, none of 22 patients with previous surgery presented with tumor growth; one of 41 patients treated with bromocriptine presented with symptoms requiring drug resumption. In patients with macroprolactinomas, none of 21 patients with previous surgery presented with tumor growth, while 11 of 30 patients treated with pregestational bromocriptine noted clinical symptoms during pregnancy.

56. (2) **Colao A,** et al. Pregnancy outcomes following cabergoline treatment: extended results from a 12-year observational study. Clin Endocrinol (Oxf) 2008;68:66–71.

A prospective observational study reporting pregnancy outcomes in 380 pregnancies in women treated with cabergoline. Fetal exposure to cabergoline through early pregnancy does not induce any increased risk of congenital malformation or miscarriage.

57. (3) **Turkalj I,** et al. Surveillance of bromocriptine in pregnancy. JAMA 1982;247:1589–1591.

Information was collected on the outcome of 1,410 pregnancies in 1,335 women to whom bromocriptine had been given, primarily in the early weeks of pregnancy. The incidence rate of spontaneous abortions, extrauterine pregnancies, and minor and major malformations is comparable with that quoted for normal populations.

Acromegaly

58. (4) **Melmed S. Acromegaly. N** Engl J Med 2006;355:2558–2573

Comprehensive review article on the topic, updating the author's previous review

59. (4) **Melmed S.** Acromegaly pathogenesis and treatment. J Clin Invest 2009;119:3189–3202

This review discusses the pathophysiology of GH and GH-secreting pituitary adenomas and treatment options for acromegaly.

60. (4) **Melmed S,** et al. Guidelines for acromegaly management. J Clin Endocrinol Metab 2009;94:1509–1517.

The Acromegaly Consensus Group has updated their 2002 recommendations for acromegaly management in this evidence-based report.

61. (4) **Giustina A,** et al. A consensus on criteria for cure of acromegaly. J Clin Endocrinol Metab 2010;95:3141–3148.

The Acromegaly Consensus Group has revised evidence-based definitions for active acromegaly and disease control, updating their 2000 guidelines.

62. (2) **Swearingen B,** et al. Long-term mortality after transsphenoidal surgery and adjunctive therapy for acromegaly. J Clin Endocrinol Metab 1998;83:3419–3426.

In this retrospective review of 162 patients, surgical cure was seen in 91% of microadenomas and in 48% of macroadenomas. Adjunctive therapy was required in 40%. Biochemical remission was achieved in 83% at a mean of 7.8 years. Mortality regression analysis of patients cured with surgery approached age- and gender-matched US population samples.

63. (*2*) **Kreutzer J,** et al. Surgical management of GH-secreting pituitary adenomas: An outcome study using modern remission criteria. J Clin Endocrinol Metab 2001;86: 4072–4077.

This retrospective analysis of 57 patients, at a mean of 37.7 months postoperatively, revealed remission by normal IGF-1 in 70.2%, random GH less than 2.5 mg/l in 66.7%, and glucose-suppressed GH less than 1 mg/l in 61.1%. Tumor size at diagnosis predicted persistence of disease.

64. (2) **Nomikos P,** et al. The outcome or surgery in 668 patients with acromegaly using current criteria of biochemical 'cure.' Eur J Endocrinol 2005;152:379–387.

This series of 688 consecutive patients treated over 19 years revealed 57% of all patients treated with transsphenoidal surgery achieved biochemical control defined as GH less than 1 ng/ml post–glucose load and normal IGF-1 levels. Microadenomas were controlled in 75% of cases, and macroadenomas had lower cure rates based on size and invasion characteristics. Suprasellar tumors without visual compromise were cured in 45% of cases, suprasellar tumors with visual compromise in 33%, and giant adenomas (≥40 mm diameter) in 10%.

65. (2) **Barker F,** et al. Transsphenoidal surgery for pituitary tumors in the United States, 1996–2000: Mortality, morbidity, and the effects of hospital and surgeon volume. J Clin Endocrinol Metab 2003;88:4709–4719.

This retrospective analysis of 5,497 pituitary operations revealed that higher-volume hospitals and neurosurgeons had better short-term outcomes after transsphenoidal surgery.

66. (2) **Bates P,** et al. Wide variation for surgical outcomes for acromegaly in the UK. Clin Endoc (Oxf) 2008;68:136–142

This prospective and retrospective observational study of more than 1,200 cases of acromegaly collected over 34 years assessed achievement of target levels of GH and IGF-1 at 1 year post–transphenoidal surgery. Success rates were significantly greater after 2000 when surgery was concentrated over a smaller number of surgeons.

67. (4) **Katznelson L.** Approach to the patient with persistent acromegaly after pituitary surgery. J Clin Endocrinol Metab 2010;95:4114–4123.

This case-centered review article discusses treatment options for patients who do not reach cure hormone levels after initial pituitary surgery.

68. (4) **Murray R, Melmed S.** A critical analysis of clinically available somatostatin analog formulations for therapy of acromegaly. J Clin Endocrinol Metab 2008;93:2957–2968.

Review of multiple studies evaluating the efficacies of available long-acting preparations of octreotide LAR, lanreotide SR, and lanreotide ATG revealed generally equal control of clinical symptoms and GH and IGF-1 levels with octreotide LAR and lanreotide ATG. The lanreotide ATG is given by deep subcutaneous, whereas the other preparations require IM administration, offering an advantage versus lanreotide SR with comparable efficacy. Lanreotide SR is dosed at 10- to 14-day intervals, while other preparations are dosed every 28 days.

69. (1) **Newman C,** et al. Octreotide as primary therapy for acromegaly. J Clin Endocrinol Metab 1998;83:3034–3040.

This multicenter study using daily octreotide compared 26 patients receiving primary octreotide with 81 receiving adjunctive therapy. Responders were defined as having GH levels decreasing to at least two standard deviations below baseline mean GH. No significant difference was found in response rates in the primary (70%) and adjunctive (60%) groups. Both groups achieved similar improvement in clinical symptoms during 3 years of follow-up.

70. (*1*) **Colao A,** et al. Long-term effects of depot long-acting somatostatin analog octreotide on hormone levels and tumor mass in acromegaly. J Clin Endocrinol Metab 2001;86:2779–2786.

Depot octreotide was given to 36 patients, 15 de novo and in 21 who had previously been surgically treated, for up to 24 months. Including both groups, GH below 2.5 mg/l was seen in 69.4%, whereas IGF-1 levels were normal in 61.1% at last observation. Similar percentages were achieved for both groups. Tumor volume decreased in 12 of 15 in the de novo group and 5 of 9 in the operated-on group.

71. (4) **Melmed S,** et al. A critical analysis of pituitary tumor shrinkage during primary medical therapy in acromegaly. J Clin Endocrinol Metab 2005;90:4405–4410.

This systematic literature review highlights the efficacy of SSAs in decreasing tumor size as primary therapy or before surgery or radiation therapy.

72. (*2*) **Abe T, Ludecke.** Effects of preoperative octreotide treatment on different subtypes of 90 GH-secreting pituitary adenomas and outcome in one surgical centre. Eur J Endocrinol 2001;145:137–145.

This retrospective study compared 90 patients who received at least 3 months of preoperative daily octreotide versus 57 who had not received therapy. At a mean follow-up of 51 months, endocrine remission was achieved slightly more frequently in the pretreated group for microadenomas (100% vs. 92.9%), resectable macroadenomas (95.2% vs. 87.5%), and invasive potentially resectable macroadenomas (81.4% vs.73.9%).

73. (*1*) **Kristof RA,** et al. Does octreotide treatment improve the surgical results of macroadenomas in acromegaly? Acta Neurochir 1999;141:399–405.

This prospective controlled study evaluated surgical outcomes in 13 octreotide-treated patients versus 11 controls. Therapy was given for a mean of 16 weeks preoperatively. Postoperative remission rates were not significantly different in the treated (55%) versus untreated controls (69%).

74. (4) **Ben-Shlomo A, Melmed S.** The role of pharmacotherapy in perioperative management of patients with acromegaly. J Clin Endocrinol Metab 2003;88:963–966.

This review discusses SSA therapy before resection of somatotroph adenomas or nonpituitary surgery requiring anesthesia in patients with acromegaly. Effects on postoperative IGF-1 and GH control rates and cardiovascular, pulmonary, and glycemic parameters are evaluated.

75. (1) **Carlsen S,** et al. Preoperative octreotide treatment in newly diagnosed acromegalic patients with macroadenoma increases short-term post operative cure rates: a prospective randomized trial. J Clin Endocrinol Metab 2008;93:2984–2990

The POTA trial assessed the effect of 6 months preoperative octreotide every 28 days versus no SSA on IGF-1 levels 3 months post-op. Patients with macroadenomas treated preoperatively with octreotide reached cure range IGF-1 levels in 50% of cases versus 16% in the control group. No improvement in cure rates was seen in microadenoma patients.

76. (*2*) **Barrande G,** et al. Hormonal and metabolic effects of radiotherapy in acromegaly: Long-term results in 128 patients followed in a single center. J Clin Endocrinol Metab 2000;85:3779–3785.

Conventional external beam radiation therapy was delivered to 128 patients in this retrospective single-center study. Basal GH less than 2.5 mg/l was seen in 35% at 5 years, 53% at 10 years, and 66% at 15 years. At 10 years, relative deficiencies were seen in gonadotropins in 80%, TSH in 78%, and ACTH in 82%.

77. (4) **Laws E,** et al. Stereotactic radiosurgery for pituitary adenoma: A review of the literature. J NeuroOncol 2004;69:257–272.

Stereotactic radiosurgery can lead to a more rapid normalization of hormone levels with a lessened chance of hypopituitarism, radiation-induced neoplasia, and cerebrovascular injury when compared with fractionated radiation therapy.

78. (2) **Petit J,** et al. Proton stereotactic radiosurgery in management of persistent acromegaly. Endocr Pract 2007;13:726–734.

This prospective trial followed 22 patients with acromegaly persistent after surgery treated with proton beam therapy. After a median follow-up of 6.3 years, 59% achieved normal IGF-1 levels, and 38% had developed deficits of other pituitary hormones. No second tumors or vision defects were noted.

79. (2) **Abs R,** et al. Cabergoline in the treatment of acromegaly: A study in 64 patients. J Clin Endocrinol Metab 1998;83:374–378.

This prospective open-label study revealed IGF-1 less than 300 mg/l in 39%. If tumors secreted both GH and PRL, the level of IGF-1 was less than 300 mg/l in 50%. In the subset of patients with initial IGF-1 less than 750 mg/l, 53% achieved an IGF-1 level less than 300 mg/l. Duration of treatment was between 3 and 40 months.

80. (3) **Moyes V,** et al. Clinical use of cabergoline as primary and adjunctive treatment for acromegaly. Eur J Endocrinol 2008;159:541–545.

In this prospective chart audit, 15 patients with acromegaly with median IGF-1 471 ng/ml and median GH 9.7 mIU/l received cabergoline with median dose 1.75 mg/wk. Thirty-three percent achieved normal IGF-1 levels, and 27% achieved both normal IGF-1 and GH levels with observation duration of 2 to 52 weeks.

81. (*1*) **Trainer PJ,** et al. Treatment of acromegaly with the growth hormone-receptor antagonist pegvisomant. N Engl J Med 2000;342:1171–1177.

IGF-1 decreased by 50.1% (626.7%) in the 15-mg SC daily group and 62.5% (621.3%) in the 20-mg group in this 12-week randomized double-blind study. Normal IGF-1 was achieved in 81% of the 15-mg/d group and 89% of the 20-mg/d group.

82. (*2*) **Van der Lely AJ,** et al. Long-term treatment of acromegaly with pegvisomant, a growth hormone receptor antagonist. Lancet 2001;358:1754–1759.

Pegvisomant was given for 6 to 18 months. IGF-1 decreased 50% or more in all groups, with normal IGF-1 levels in 97% of those treated for at least 12 months.

83. (2) **Bunk J,** et al. Tumor volume of growth hormone secreting adenomas during treatment with pegvisomant: A prospective multicenter study. J Clin Endocrinol Metab 2010;95:552–558.

This prospective study evaluated 61 acromegalic patients treated with pegvisomant. Three patients (4.9%) had increases in volume of tumor greater than 25% in the first year. Each of these patients had been treated with octreotide before study onset, leading authors to suspect that increase in volume may have related to a rebound from past decreases in tumor size caused by the octreotide.

84. (3) **Schreiber,** et al. Treatment of acromegaly with the GH receptor antagonist pegvisomant in clinical practice: safety and efficacy from the German Pegvisomant Observational Study. Eur J Endocrinol 2007;156:75–82.

This observational surveillance study followed 229 patients with persistent acromegaly previously treated with surgery, radiation, or medications. Seventy-one percent achieved normal IGF-1 levels at 12 months and 76% at 24 months. Pituitary mass volume increased in 5.2%, and liver tests rose to greater than 3× upper limit normal in 5.2%

Diabetes Insipidus

85. (2) **Hadjizacharia P,** et al. Acute diabetes insipidus in severe head injury: a prospective study. J Am Coll Surg 2008;207:477–484.

This prospective study of 436 patients with severe head trauma revealed that DI occurred in 15.4% of these patients and was associated with increased mortality. Independent risk factors for DI included high severity of injury on the Abbreviated Injury Score, cerebral edema, and Glasgow Coma Scale less than or equal to 8.

86. (2) **Pivonello R,** et al. Central diabetes insipidus and autoimmunity. J Clin Endocinol Metab 2003;88:1629–1636.

Central DI is considered idiopathic in approximately 33% of cases. This study evaluated 150 cases of CDI including 64 believed to be idiopathic. Autoantibodies to AVP-secreting cells were present in 33% of the idiopathic cases, with the greatest likelihood of this autoimmunity being present in patients with onset of disease at younger than 30 years, history of other autoimmune conditions, and pituitary stalk thickening on MRI.

87. (4) **Sands J, Bichet D.** Nephrogenic diabetes insipidus. Ann Intern Med 2006;144:186–194.

Review of the physiology, genetics, etiologies, and treatments of NDI

88. (3) **Brewster U, Hayslett J.** Diabetes insipidus in the third trimester of pregnancy. Obstet Gynecol 2005;105:1173–1176.

This report of two cases of DI in late pregnancy reviews the pathogenesis, clinical presentation, and treatment of this condition.

89. (2) **Garofeanu C,** et al. Causes of reversible nephrogenic diabetes insipidus: A systematic review. Am J Kidney Dis 2005;45:626–637.

This review of 155 studies found that the most common reversible causes of NDI were medications. Lithium, antibiotics, antifungals, antineoplastic agents, and antivirals were leading causes. Hypercalcemia and hypokalemia also were reversible causes. NDI usually resolved with withdrawal of the medication or correction of the metabolic abnormality; however, NDI due to long-term lithium therapy was commonly irreversible.

90. (4) **Robertson G.** Antidiuretic hormone: Normal and disordered function. Endocrinol Metab Clin North Am 2001;30:671–694.

This thorough review describes the physiology of antidiuretic hormone and the disease states that result from abnormal function of this substance.

Cushing Disease

91. (2) **Lindholm J,** et al. Incidence and late prognosis of Cushing's syndrome: A population-based study. J Clin Endocrinol Metab 2001;86:117–123.

The aim of the study was to assess the incidence and late outcome of CS, especially that of CD. Information was collected on patients diagnosed with CS in Denmark over a period of 11 years. The annual incidence was noted to be 1.2 to 1.7 per million people for CD, 0.6 per million for adrenal adenoma, and 0.2 per million for adrenal carcinoma. Of 139 patients with nonmalignant disease, 11.1% died during follow-up. Excessive mortality was observed mainly during the first year. The perceived quality of health was decreased in patients with CD.

92. (4) **Arnaldi G,** et al. Diagnosis and Complications of Cushing's Syndrome: A Consensus Statement. J Clin Endocrinol Metab 2003;88:5593–5602.

In October 2002, a workshop was held in Ancona, Italy, to reach a consensus on the management of CS. The consensus statement on diagnostic criteria and the diagnosis and treatment of complications of this syndrome reached at the workshop was summarized in the paper.

93. (4) **Newell-Price J,** et al. The Diagnosis and Differential Diagnosis of Cushing's Syndrome and Pseudo-Cushing's States. Endocr Rev 1998;19:647–672.

A comprehensive review of the different tests in the diagnosis of CS

94. (2) **Newell-Price J,** et al. Optimal response criteria for the human CRH test in the differential diagnosis of ACTH-dependent Cushing syndrome. J Clin Endocrinol Metab 2002;87:1640–1645.

One hundred fifteen consecutive patients with proven ACTH-dependent CS were studied, 101 with CD and 14 with EAS. The response to human corticotropin-releasing hormone (hCRH) was also studied in 30 normal volunteers with no clinical evidence of CS, and the results were compared. After basal sampling at 15 and 0 minutes, hCRH (100 μg, IV) was administered at 9 a.m., and serum cortisol and ACTH were measured at 15-minute intervals for 2 hours. The results were then analyzed to determine the sensitivity and specificity of the test.

95. (2) **Dichek HL,** et al. A comparison of the standard high dose dexamethasone suppression test and the overnight 8-mg dexamethasone suppression test for the differential diagnosis of adrenocorticotropin-dependent Cushing's syndrome. J Clin Endocrinol Metab 1994;78:418–422.

Forty-one patients who were subsequently proven at surgery to have CS were studied (34 CD and 7 EAS). HDDST and the 6-day HDDST (including a 2-day HDDST) were done on these patients. Optimal criteria for the diagnosis of CD were developed for both tests.

96. (2) **Tyrrell J,** et al. An overnight high-dose dexamethasone suppression test for rapid differential diagnosis of Cushing's syndrome. Ann Intern Med 1986;104(2):180–186.

An HDDST was performed in 76 patients with surgically or pathologically proven CS. Suppression of plasma cortisol levels to less than 50% of baseline indicated a diagnosis of Cushing disease. The test had a sensitivity of 92%, a specificity of 100%, and a diagnostic accuracy of 93%. These values equal or exceed those of the standard 2-day test whether based on suppression of urinary 17-hydroxycorticosteroids or plasma cortisol.

97. (2) **Hall WA,** et al. Pituitary magnetic resonance imaging in normal human volunteers: Occult adenomas in general population. Ann Intern Med 1994;120:817–820.

High-resolution MRI scans of 100 normal volunteers and 57 patients with CD were evaluated independently by three blinded reviewers to determine the prevalence of focal lesions of the pituitary gland that suggest the presence of pituitary adenoma in people with no symptoms. In patients with CD, abnormalities in the pituitary MRI were reported in about 56% of cases, but not all these abnormalities correlated with surgical findings. Ten percent of normal volunteers had abnormalities in pituitary MRI.

98. (2) **Oldfield EH,** et al. Petrosal sinus sampling with and without corticotrophin-releasing hormone for the differential diagnosis of Cushing syndrome. N Engl J Med 1991;325:897–905.

A prospective study of 281 patients with CS was done to evaluate the BIPSS. Bilateral sampling was successfully accomplished in 278 patients, with no major morbidity; 262 of these patients underwent sampling before and after administration of ovine CRH. The diagnosis of 246 patients was confirmed surgically. The results were then compared to evaluate the sensitivity and specificity of the test.

99. (2) **Ilias I,** et al. Jugular venous sampling: an alternative to petrosal sinus sampling for the diagnostic evaluation of adrenocorticotropic hormone-dependent Cushing's syndrome. J Clin Endocrinol Metab 2004;89:3795–3800.

This study included 74 patients with surgically proven CD, 11 with surgically confirmed, and three with occult EAS. Patients underwent JVS and inferior petronasal sinus sampling (IPSS) with administration of CRH on separate days. Ratios of central-to-peripheral ACTH in venous samples were calculated. At 100% specificity, BIPSS correctly identified 61 of 65 patients with CD [sensitivity, 94%]. When patients with abnormal venous drainage were excluded, sensitivity was 98%. JVS had a sensitivity of 83% and 100% specificity. They concluded that centers with limited sampling experience may choose to use the simpler JVS and refer patients for IPSS when the results are negative.

100. (4) **de Herder WW, Lamberts SW.** Tumor localization—the ectopic ACTH syndrome. J Clin Endocrinol Metab 1999;84:1184–1185.

This editorial discusses the results of the recent major studies investigating advance imaging techniques to localize ectopic ACTH syndrome. The editors conclude that since no single

imaging technique has optimal accuracy in the localization of ectopic ACTH-secreting tumors, combinations of conventional radiology and ^{111}In-pentreotide scintigraphy should presently be employed to optimize the chance of locating the tumor.

101. (2) **Ilias I,** et al. Cushing's syndrome due to ectopic corticotropin secretion: Twenty years' experience at the National Institute of Health. J Clin Endocrinol Metab 2005;90:4955–4962.

A study was performed at a tertiary care clinical research center that reflects their experience with EAS from 1983 to 2004. This includes 90 patients, aged 8 to 72 years, including 48 females, who were included in the study. Imaging localized tumors in 67 of 90 patients. Surgery confirmed an ACTH-secreting tumor in 59 of 66 patients and cured 65%. This article also described the characteristics of the biochemical testing in EAS and the mortality rate.

102. (2) **Pacak K,** et al. The role of [(18)F]fluorodeoxyglucose positron emission tomography and [(111)In]-diethylenetriaminepentaacetate-D-Phe-pentetreotide scintigraphy in the localization of ectopic adrenocorticotropin-secreting tumors causing Cushing's syndrome. J Clin Endocrinol Metab 2004;89:2214–2221.

This study evaluated whether [(18)F]-FDG PET or [(111)In]-diethylenetriaminepentaacetate-D-Phe-pentetreotide (OCT) at higher than standard doses of radionuclide (18 mCi; H-OCT), can localize EAS in patients with CS. Seventeen patients with presumed EAS based on inferior petrosal sinus sampling results underwent routine anatomical imaging studies (CT and MRI) and OCT scintigraphy with 6 mCi (L-OCT). Research studies included FDG-PET in all patients and H-OCT if L-OCT was negative.

The sensitivity of CT and combined H- and L-OCT scintigraphy was higher (both 53%; 95% CI, 29%–76%) than that of MRI (37%; 95% CI, 16%–64%) or FDG-PET (35%; 95% CI, 15%–61%). L-OCT was a useful complementary modality to CT and MRI. H-OCT should be considered only when other imaging modalities fail to localize the ACTH-secreting tumor in patients with EAS.

103. (2) **Swearingen B,** et al. Long-term mortality after transsphenoidal surgery for Cushing's disease. Ann Intern Med 1999;130:821–824.

A total of 161 patients (129 women and 32 men; mean age, 38 years) were treated for CD between 1978 and 1996. All had transsphenoidal adenomectomy with or without adjunctive therapy. The cure rate for microadenoma was 90%. There were no perioperative deaths. Long-term survival rates were similar to those of controls matched for age and gender.

104. (2) **Hammer G,** et al. Transsphenoidal Microsurgery for Cushing's Disease: Initial Outcome and Long-Term Results. J Clin Endocrinol Metab 2004;89:6348–6357.

A retrospective analysis of patients who had transsphenoidal microsurgery for CD. A median follow-up was obtained for 11.1 year. They mentioned the initial cure rate and the risk factors associated with low cure. The long term mortality was higher in patients with persistent disease compared to the general population, while it was the same in patients with initial cure.

105. (2) **Bachicchio D,** et al. Factors influencing the immediate and late outcome of Cushing's disease treated by transsphenoidal surgery: A retrospective study by the European Cushing's Disease Survey Group. J Clin Endocrinol Metab 1995;80:3114–3119.

A retrospective survey of 668 patients treated at 25 European centers. The surgical mortality rate was 1.9%, the major surgical morbidity was 14%, and the initial cure rate was 76%. The long-term cure rate was 67% during 6 to 104 months of follow-up.

106. (2) **Estrada J,** et al. The complete normalization of the adrenocortical function as the criterion of cure after transsphenoidal surgery for Cushing's disease. J Clin Endocrinol Metab 2001;86(12):5695–5699.

Fifty-eight patients with corrected hypercortisolism after transsphenoidal surgery for Cushing disease were studied. Patients were classified in three groups: group I, patients with transient hypocortisolism and normal HPA afterward; group II, patients with transient hypocortisolism and abnormalities in the circadian rhythm or the stress response afterward; and group III, patients without postoperative hypocortisolism. Groups I and II were similar in postsurgical plasma cortisol (46.9 ± 30.3 vs. 60.7 ± 38.6 nM) and mean follow-up (69.8 vs. 68.8 months) but were significantly different in their recurrence rate (3.4% vs. 50%, $p < 0.001$). Patients in group III had normal postsurgical plasma and urinary cortisol but persistent abnormalities in circadian rhythm and stress response. After a mean follow-up of 39.1 months, their recurrence rate was similar to that of group II (64.7% vs. 50%). The authors suggest that complete normalization of the adrenocortical function, which is always preceded by postsurgical hypocortisolism, is associated with a very low recurrence risk and should be considered the main criterion of surgical cure in Cushing disease.

107. (4) **Morris D, Grossman A.** The medical management of Cushing's syndrome. Ann N Y Acad Sci 2002;970:119–133.

A review of the drugs available for treating excessive circulating glucocorticoids

Syndrome of Inappropriate Antidiuretic Hormone Secretion

108. (2) **Comis R,** et al. Abnormalities in water homeostasis in small cell anaplastic lung cancer. Cancer 1980;45:2414–2421.

An observational study of 41 patients with small cell lung carcinoma. All patients in the study were given a standard water load test; as a result, 68% of these patients had an abnormal test result, and 46% had clinical evidence of SIADH.

109. (3) **Sterns R,** et al. Neurologic sequelae after treatment of severe hyponatremia: A multicenter perspective. J Am Soc Nephrol 1994;4:1522–1530.

A multicenter observational study of 56 patients with serum sodium levels below 105 mmol/l that looked at side effects of therapy that corrected the hyponatremia. This study concluded that chronic hyponatremia and rapid correction within the first 2 days significantly increased the risk of complications.

110. (4) **Verbalis JG, Berl T.** Disorders of water balance. In: Brenner BM. Brenner & Rector's the kidney. Vol 1. 8th ed. Saunders, 2007:459–491.

This book chapter discusses the physiology of kidney and how it maintains water and sodium homeostasis.

111. (2) **Forrest J,** et al. Superiority of demeclocycline over lithium in the treatment of chronic syndrome of inappropriate secretion of antidiuretic hormone. N Engl J Med 1978;298:173–177.

This study compared the efficacy of demeclocycline with lithium in the treatment of 10 patients with chronic SIADH. It showed that demeclocycline is more effective in treatment of this syndrome.

112. (4) **Lehrich RW, Greenberg A.** When is it appropriate to use vasopressin receptor antagonists? J Am Soc Nephrol 2008;19:1054–1058.

This commentary discusses the current and potential indications for use of vasopressin receptor antagonist.

113. (1) **Schrier R,** et al. Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. N Engl J Med 2006;355(20):2099–2112.

In two multicenter, randomized, double-blind, placebo-controlled trials, patients were randomly assigned to oral placebo (223 patients) or oral tolvaptan (225) at a dose of 15 mg daily. Serum sodium concentrations increased more in the tolvaptan group than in the placebo group during the first 4 days ($p < 0.001$) and after the full 30 days of therapy ($p < 0.001$).

114. (4) **Decaux G,** et al. Non-peptide arginine–vasopressin antagonists: the vaptans. Lancet 2008;371(9624):1624–1632.

This review discusses the pathophysiology of hyponatremia and the uses of arginine–vasopressin–receptor agonists in euvolemic and hypervolemic hyponatremia.

115. (1) **Berl T,** et al.; SALTWATER Investigators. Oral tolvaptan is safe and effective in chronic hyponatremia. J Am Soc Nephrol 2010;21:705–712.

SALTWATER was a multicenter, open-label extension of the Study of Ascending Levels of Tolvaptan in Hyponatremia (SALT-1 and SALT-2). In total, 111 patients with hyponatremia received oral tolvaptan for a mean follow-up of 701 days. Mean serum sodium increased from 130.8 mmol/l at baseline to greater than 135 mmol/l throughout the observation period ($p < 0.001$ vs. baseline at most points). Responses were comparable between patients with euvolemia and those with heart failure but more modest in patients with cirrhosis.

116. (4) **Greenberg A, Lehrich RW.** Treatment of chronic hyponatremia: now we know how, but do we know when or if? J Am Soc Nephrol 2010;21:552–555.

This editorial discusses the SALTWATER study, which is the first long-term study investigating the use of vaptan on patients with chronic hyponatremia. The author then advocates treating chronic hyponatremia in patients who lack obvious symptoms because emerging evidence suggests it would reduce morbidity by improving alertness, reducing gait impairment and fracture.

117. (4) **Gross P.** Treatment of hyponatremia. Intern Med 2008;47(10):885–891.

This review discusses the pathophysiology of hyponatremia and the uses of arginine–vasopressin–receptor agonists in euvolemic and hypervolemic hyponatremia.

2

Thyroid Disorders

M. Regina Castro and Hossein Gharib

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EVALUATION OF THYROID FUNCTION

Thyrotropin

Thyroid-stimulating hormone (TSH), or thyrotropin, is the single most useful measurement in the evaluation of thyroid function. Produced by the anterior pituitary, TSH stimulates the thyroid gland to produce the thyroid hormones thyroxine (T4) and triiodothyronine (T3) and its secretion is, in turn, closely regulated by the serum concentrations of these hormones. This measurement has been recommended by the American College of Physicians as a screening test in women over the age of 50 years, in whom the prevalence of unsuspected hypothyroidism appears to be significant [1]. TSH determination every 5 years in women and men over the age of 35 is a cost-effective measure to detect early thyroid failure; its diagnostic yield increases with advancing age and is higher in women than men [2]. In hospitalized patients, however, screening with TSH leads to many false-positive results [3]. Although normal serum TSH reference range has long been considered to be 0.5 to 5.0 mIU/l, some authors have argued that a narrower reference range (0.5–2.5 mIU/l) more accurately reflects a true euthyroid state in the absence of other confounders, such as thyroid peroxidase antibodies (TPOAbs), medication effect, etc. [4,5]. However, this has not been universally accepted [6]. TSH distribution progressively shifts toward higher concentrations with advancing age. Because of this, age-specific range for TSH should be used to avoid overestimating the prevalence of subclinical hypothyroidism (SCH) [7]. Limitations of TSH testing include the following:

- Central hypothyroidism. Measurement of TSH alone may be misleading in these patients. Central hypothyroidism is suspected when free T4 (FT4) values are low and the TSH level is low, normal, or less elevated than would be expected in a patient with hypothyroidism [8]. In these patients, secreted TSH has reduced biologic activity but remains immunoactive in the assay [9].
- Thyrotoxicosis due to inappropriate TSH secretion. Measurement of TSH alone in patients with a TSH-secreting pituitary adenoma may be misleading. High levels of serum FT4 and T3, along with inappropriately normal or

elevated serum TSH levels, an elevated a-subunit, and finding of a pituitary adenoma on magnetic resonance imaging (MRI) will confirm the diagnosis.

- Patients treated for hyperthyroidism, in whom serum TSH levels may remain suppressed for 3 months or longer after patient is clinically euthyroid. Because of this delay in recovery of the pituitary–thyroid axis, during the first several months of treatment, clinical decisions should be based on measurement of FT4 and T3, until steady-state conditions are met.
- Drugs that affect serum TSH concentrations. Dopamine inhibits TSH and can reduce TSH levels in hypothyroid patients into the normal range. Glucocorticoids may slightly reduce TSH into the subnormal range. Acute amiodarone use can transiently increase TSH concentration.
- Patients with nonthyroidal illness [10] (see Section on Euthyroid Sick Syndrome).

Free Thyroxine

Thyroxine is extensively bound to plasma proteins, and only a very small fraction circulates in the free state. The free hormone fraction, however, determines its biologic activity, making its measurement diagnostically more relevant than the total serum level because of the many binding protein abnormalities that can alter total thyroid hormone levels, independent of thyroid status. Although many methods of estimation of serum FT4 concentration are available, none—including equilibrium dialysis and ultrafiltration, regarded as the standard criterion or reference methods—gives a true indication of the effects of binding competitors that inhibit binding of T4 to thyroxine-binding globulin [11].

Total Thyroxine and Triiodothyronine

Serum total T4 and T3 values reflect not only thyroid hormone production but also serum levels of thyroid hormone–binding proteins. Discrepancy between normal serum free and high total thyroid hormone concentrations usually reflect elevated levels of binding proteins, a condition commonly referred to as "euthyroid hyperthyroxinemia." T3 estimation is most useful when FT4 values are normal and TSH levels are suppressed (T3 toxicosis and subclinical hyperthyroidism) [12]. In euthyroid patients with acute medical illness, low T3 levels may reflect decreased peripheral conversion of T4 to T3. A high T3:T4 ratio (>20 ng/μg) suggests Graves disease as the underlying cause of hyperthyroidism.

Thyroid Autoantibodies

The test for TPOAbs is the most sensitive measurement for autoimmune thyroid disease. When it is measured by a sensitive assay, over 95% of patients with Hashimoto thyroiditis and 85% of patients with Graves disease have detectable levels of TPOAbs [12]. Also, the presence of TPOAbs is also predictive of future development of hypothyroidism, even in patients with normal serum TSH levels [13].

TSH receptor antibodies (TRAbs) can be found in most patients with Graves disease, although such determination is seldom necessary to confirm the diagnosis. TRAbs may be predictive of the risk of relapse of Graves hyperthyroidism after treatment with antithyroid drugs (ATDs) [14]. TRAbs are also useful in predicting fetal and neonatal thyroid dysfunction in pregnant women with a history of autoimmune thyroid disease [15].

Thyroglobulin antibody (TgAb) measurement is used primarily as an adjunct test to serum thyroglobulin (Tg) in the follow-up of patients with differentiated thyroid cancer because even very low levels of these antibodies can interfere with Tg determination causing falsely low or high values [16]. The sudden rise or appearance of TgAbs in a previously negative TgAb patient may be the first indication of recurrence [12].

Thyroglobulin

Thyroglobulin is the precursor of thyroid hormone synthesis and is present in the serum of all unaffected people. Serum thyroglobulin (Tg) concentrations reflect three factors: the mass of differentiated thyroid tissue; any physical damage or inflammation of the thyroid gland; and the level of TSH receptor (TSHR) stimulation, given that most steps in Tg biosynthesis and secretion are TSH dependent [17]. An elevated Tg level is a nonspecific indicator of thyroid dysfunction. Tg is helpful in distinguishing factitious hyperthyroidism, resulting from exogenous thyroid hormone administration and from endogenous hyperthyroidism, because in the former case, serum Tg levels are usually low, whereas in the latter, serum Tg concentrations are typically increased. Tg measurement is primarily used as a tumor marker in the follow-up of patients with differentiated thyroid cancer after thyroidectomy to detect recurrent or metastatic disease. Serum Tg, measured during TSH stimulation—endogenous TSH after thyroid hormone withdrawal or recombinant human TSH (rhTSH)—is more sensitive for detecting differentiated thyroid cancer than basal Tg measured during levothyroxine (LT4) suppressive therapy [18].

Tg measurement has also been used in recent years to confirm the presence of metastatic thyroid cancer in needle washouts after fine-needle aspiration (FNA) biopsy of suspicious cervical lymph nodes (CLNs) in patients with a history of thyroid cancer [19,20]. It has been found to be more sensitive than FNA cytology of lymph nodes (LNs) and has the advantage of not being affected by the presence of anti-Tg antibodies in the serum [19].

THYROID IMAGING

Ultrasonography

Ultrasonography (US) is the test of choice for evaluation of thyroid size and morphology; it is the most sensitive test in the detection of thyroid nodules, capable of detecting lesions 2 to 3 mm in diameter. It is also useful in guiding FNA biopsy of palpable and nonpalpable thyroid nodules. US features predictive of malignancy in thyroid nodules include: hypoechogenicity; presence of microcalcifications; a thick, irregular, or absent halo; irregular margins; regional adenopathy; and intranodular vascular spots [21,22]. US cannot, however, unequivocally distinguish benign from malignant nodules, and FNA is needed to confirm the diagnosis. US is also used for evaluation of regional LNs, both in the preoperative assessment and in the postoperative surveillance of thyroid cancer. It has been found in some studies to be more sensitive than other surveillance modalities such as Tg measurement and whole-body scanning (WBS) [23]. The major limitations of US are the high degree of observer dependency and its inability to visualize retrotracheal, retroclavicular, or intrathoracic lesions.

Scintigraphy

Scintigraphy is the standard method for functional imaging of the thyroid, and two isotopes most commonly used are iodine 123 (^{123}I) and ^{99m}Tc-pertechnetate; the latter has the advantage of lower cost and greater availability. ^{99m}Tc scanning provides a measure of the iodine-trapping function in the thyroid or in a nodule within the gland. Thyroid scanning is commonly used to demonstrate that a palpable enlargement represents an entire lobe rather than a nodule; localize functional thyroid tissue; identify the cause of hyperthyroidism: homogeneously increased uptake in Graves disease, irregular uptake in multinodular goiter or thyroid nodules; identify functioning thyroid nodules: because "hot" or hyperfunctioning nodules are rarely malignant, such finding would obviate the need for FNA biopsy; and follow the evolution of characteristics of nodular goiter [24].

Computed Tomography

Computed tomography (CT) scans are useful in the evaluation of thyroid cancer recurrence, especially in delineating the extent of retrosternal involvement and defining the presence and extent of lymph node (LN) metastases, tracheal invasion, compression or displacement, and vascular invasion. CT is also helpful in assessing tumors not clearly arising from the thyroid and bulky tumors with possible invasion of local structures. CT is less sensitive than US in detecting intrathyroidal lesions.

Radioiodine Uptake

The main role of radioiodine (RAI) uptake is in the evaluation of hyperthyroidism, to distinguish subacute or silent thyroiditis from toxic goiter, to provide data to determine whether RAI therapy is feasible, and, if so, to aid in the dose calculation. Thyroid uptake reflects a combination of iodine transport into the thyroid follicular cells, its oxidation and organification, and its release from the thyroid. Increased uptake is usually seen in association with hyperthyroidism; Hashimoto thyroiditis; iodine deficiency; subacute, silent, or postpartum thyroiditis in the recovery phase; choriocarcinoma and hydatidiform mole; and during treatment with lithium carbonate. Decreased uptake occurs after treatment with iodine-containing substances; in the thyrotoxic phase of subacute, silent, or postpartum thyroiditis; Hashimoto thyroiditis with widespread parenchymal destruction; thyroid agenesis, or after therapeutic ablation; and with the use of ATDs [24].

^{131}I Whole-Body Scanning

^{131}I WBS is used early in the diagnostic work-up of patients with suspected recurrent or metastatic thyroid cancer. Withdrawal of thyroid hormone therapy and a low iodine diet have been traditionally used to raise TSH concentration and increase uptake by thyroid tissue. Its sensitivity varies widely between studies, averaging 50% to 60%, depending on the dose of the isotope used, and site of tumor location, being highest for bone and lung, and lowest in LN metastases [25]; its overall specificity is high (90%–100%) [26]. When used in combination with Tg measurement after TSH stimulation, its sensitivity increases substantially, detecting up to 93% of cases with disease or tissue limited to the thyroid bed and 100% of cases with metastatic disease [18]. More recently, rhTSH has been used effectively to stimulate RAI uptake for WBS in patients with suspected recurrent thyroid cancer [27], and results have been comparable to those obtained after thyroid hormone withdrawal [28].

^{18}F-Fluorodeoxyglucose Positron Emission Tomography

This imaging modality has been found to be most useful in patients with suspected recurrent or metastatic thyroid cancer, in whom other imaging modalities, such as ^{131}I WBS, have failed to localize the tumor [29]. Its sensitivity in such cases approaches 94% and its specificity 95% [30]. It is particularly helpful in patients with Hürthle cell carcinomas, in whom one study found it to be more sensitive than WBS [31]. ^{18}F-Fluorodeoxyglucose positron emission tomography (FDG-PET) is especially useful in evaluating patients with elevated Tg levels and normal RAI WBS (scan negative, Tg positive). When combined with CT, it is a more sensitive method in the follow-up of thyroid cancer recurrence or metastases, particularly in those with negative WBS [32].

HYPERTHYROIDISM

Definition

Hyperthyroidism is a syndrome that results from the metabolic effects of sustained excessive circulating concentrations of thyroid hormones, T4, T3, or both. Subclinical hyperthyroidism refers to the combination of undetectable serum

TSH concentration and normal serum T3 and T4 concentrations, regardless of the presence or absence of clinical symptoms.

Etiology

Hyperthyroidism may result from endogenous hormone overproduction alone or in combination with secretion of thyroid hormones or may be iatrogenic, as a result of administration of thyroid hormones or other drugs capable of inducing thyroiditis. The most common causes of endogenous hyperthyroidism include Graves disease, toxic multinodular goiter, toxic adenoma, and thyroiditis. Subacute thyroiditis can present in a painful (granulomatous) form, viral in origin, and a painless form, which may occur sporadically, or more commonly in the postpartum period. In this condition, a high prevalence (50%–80%) of TPOAbs in patients' sera, evidence of lymphocytic infiltration of the gland, and frequently in association with other autoimmune diseases, suggests an autoimmune etiology. Exogenous thyroid hormone, given as suppressive therapy for thyroid cancer or benign thyroid nodules, or due to overreplacement in hypothyroid patients, or surreptitious use in others, may result in overt or subclinical hyperthyroidism.

Epidemiology

Graves disease accounts for between 60% and 80% of patients with hyperthyroidism. It is up to 10 times more common in women, with highest risk of onset between the ages of 40 and 60 years. Its prevalence is similar among whites and Asians and lower among blacks [33]. Autonomous adenomas and toxic multinodular goiter are more common in Europe and other areas of the world where residents are likely to experience iodine deficiency; their prevalence is also higher in women and in patients older than age 60 years.

Pathophysiology

Graves disease is an autoimmune disorder in which autoantibodies bind to and stimulate the thyroid stimulating hormone receptor (TSHR), resulting in increased intracellular cyclic adenosine monophosphate (cAMP) levels with subsequent thyroid growth, goiter formation, and increased thyroid hormone synthesis and secretion. With the use of more sensitive assays, these antibodies have been found in over 90% of patients with Graves disease. The pathogenesis of toxic nodular goiter is an area of active investigation. Thyroid autonomy has been postulated as the main pathogenic mechanism in toxic adenomas and is thought to be due to somatic mutations that constitutively activate the cAMP cascade. Such mutations have been clearly described [34], and in some cases of multinodular goiter, several mutations have been documented in the same patient. Other growth factors, iodine intake, and immune mechanisms may also contribute to the pathogenesis of toxic multinodular goiter.

Diagnosis

Classic manifestations of hyperthyroidism include nervousness, irritability, tremor, fatigue, tachycardia or palpitations, heat intolerance, and weight loss, often despite increased appetite. Atrial fibrillation, cardiac failure, and weakness are also common in older patients. In addition to these symptoms, Graves disease usually presents with a finding of a firm, diffuse goiter in up to 90% of patients, ophthalmopathy in about 50%, and in 1% to 2% a localized dermopathy over the anterolateral aspects of the shin [33]. In patients with toxic adenoma, a palpable nodule is often found on clinical examination, whereas in toxic multinodular goiter, a firm heterogeneous goiter of variable size is more common. Some patients with multinodular goiters may have retrosternal extension. Patients with toxic adenomas or multinodular goiters may have few or no clinical symptoms and may be diagnosed only on the basis of laboratory findings. Subacute (granulomatous)

thyroiditis may present with an exquisitely tender thyroid gland, often preceded by a viral upper respiratory infection, or in its more common, painless form, seen in the postpartum period, present with transient hyperthyroidism, followed by a variable period of hypothyroidism and subsequent spontaneous resolution.

Laboratory findings in hyperthyroidism are summarized in Table 2.1. Suppressed TSH and elevated FT4 and FT3 levels are seen in overt hyperthyroidism, but in subclinical hyperthyroidism, serum FT4 and FT3 concentrations are typically normal. When Graves disease is suspected but the diagnosis remains uncertain, measurement of TRAb may be helpful. Patients with symptoms of hyperthyroidism, elevated FT3 and FT4 levels, and normal or elevated TSH (inappropriate TSH secretion) may have a pituitary TSH-secreting tumor, or selective pituitary resistance to thyroid hormone. Similar findings, in the absence of signs or symptoms of hyperthyroidism, may be seen in syndromes of generalized resistance to thyroid hormone. RAI uptake and scan are useful in determining the etiology of hyperthyroidism. Increased uptake in a homogeneous pattern is seen in Graves disease, whereas in subacute thyroiditis and hyperthyroidism due to exogenous thyroid hormone administration, the uptake is usually low. Patients with toxic adenomas demonstrate a localized area of increased uptake, whereas in multinodular goiter, uptake may be normal but the pattern heterogeneous.

Treatment

Antithyroid Drugs

Antithyroid drugs (ATDs) are the treatment of choice for Graves disease in most countries in the world. The most commonly used in the United States are methimazole at doses from 10 to 40 mg once daily and propylthiouracil (PTU) in doses starting at 100 to 150 mg every 8 hours. PTU is no longer a first-choice drug because of recent reports of severe hepatotoxicity. When treating hyperthyroidism, the lowest dose needed to achieve and maintain clinical euthyroidism should be used because higher doses have not been shown to decrease relapse rates but may increase frequency of adverse effects [35]. Methimazole has the advantage of lower toxicity [36] (particularly when used in lower doses) and longer half-life, allowing single daily dosing, which usually results in increased adherence and more rapid decline in thyroid hormone levels, and is now recommended as the first-line ATD in most patients, whereas PTU is preferred during the first trimester of pregnancy since it is thought to be less likely to cross the placenta and because methimazole has been associated with certain rare congenital anomalies, such as choanal atresia and aplasia cutis [37]. Their major disadvantage is the high incidence of relapse of hyperthyroidism (up to 60%) after discontinuation of therapy. Optimal duration of therapy is between 12 and 18 months [38]. Prolonging treatment beyond 18 months does not seem to provide additional benefits [39,40]. Long-term treatment appears to be safe [41] and a reasonable option for patients whose hyperthyroidism can be controlled with a low dose of these drugs [42].

Antithyroid Drugs plus LT4

A study from Japan reported a significant reduction in relapse (from 35% to 2%) with the addition of LT4 after 6 months of treatment with methimazole (block-replace regimen), and continuing this drug for 3 years after methimazole was stopped [43]. A subsequent study failed to confirm these findings [44]. The titration (low dose) regimen had fewer adverse effects than the block-replace (high dose) regimen and was equally effective. Continued thyroxine treatment following initial antithyroid therapy does not appear to provide any benefit in terms of recurrence of hyperthyroidism [39].

Table 2.1. Laboratory Tests for Hyperthyroidism

Etiology	Thyroid Function Tests: TSH	Thyroid Function Tests: FT4 and T3	RAI Uptake/Scan	Additional Helpful Tests
Endogenous				
Graves disease	↓↓	↑↑	Homogeneous, ↑ or N	TSI (TSAb)
Subacute thyroiditis	↓	↑	↓ RAI uptake	ESR
Toxic multinodular goiter	↓	N or ↑	Heterogeneous, N or ↑	US or CT
Toxic adenoma	↓	N or ↑	Focal increased uptake; rest of gland may have suppressed uptake	US
Pituitary TSH adenoma	N or ↑	↑	Homogeneous, ↑	Pituitary MRI; α-subunit TRH stimulation test
Exogenous				
Iodine induced (including IV dye and drugs such as amiodarone)	↓	↑	↓↓ RAI uptake	Urinary iodine excretion
Surreptitious thyroid hormone, excessive replacement or suppressive doses	↓	↑	↓ RAI uptake	Serum thyroglobulin

Although controversy exists about the usefulness of ATDs in Graves disease before definitive therapy with ^{131}I, such treatment does not seem to protect against worsening thyrotoxicosis nor to affect time-to-cure or relapse rates [39,45].

Radioiodine

RAI has been used for treatment of hyperthyroidism for over six decades. It is the preferred treatment modality in the United States for patients with Graves hyperthyroidism, though used less commonly worldwide. RAI is appropriate treatment for Graves disease, toxic nodules, and toxic multinodular goiters [46]. It is effective and safe and significantly reduces thyroid volume, although patients with large goiters and severe hyperthyroidism may require several doses [47]. If RAI is used to treat Graves hyperthyroidism, sufficient radiation should be administered in a single dose (typically 10–15 mCi) to render the patient with Graves disease hypothyroid [37]. Most patients treated in this manner will require lifelong replacement with thyroid hormone. Some researchers believe that RAI therapy may transiently worsen Graves ophthalmopathy, a problem that can be prevented by administration of prednisone [48].

Surgery

Surgery is the treatment of choice for hyperthyroid patients with large goiters who have symptoms of compression, those with a coexistent suspicious thyroid nodule, for patients who have contraindications to or refuse medical therapy and RAI, and in pregnant women, whose symptoms cannot be controlled with, or who experience allergic reactions to, ATDs. It is safe and effective, with an overall success rate of 92% [49].

If surgery is chosen as the primary therapy for Graves disease, near-total or total thyroidectomy (TT) is the procedure of choice [37].

β-Blockers

β-Blockers are useful to control the adrenergic symptoms of hyperthyroidism and may be used as initial adjunctive therapy and discontinued after definitive therapy with ATDs, RAI, or surgery that have succeeded in controlling those symptoms. β-Blockers are safe and effective in the preoperative treatment of these patients and result in faster relief of hyperthyroid symptoms when compared with results of conventional preparation with ATDs [50]. They are strongly recommended in elderly patients with symptomatic hyperthyroidism and to other hyperthyroid patients with resting heart rates in excess of 90 beats per minute or coexistent cardiovascular disease.

HYPOTHYROIDISM

Definition

Hypothyroidism is a clinical syndrome that results from decreased thyroid hormone production and secretion, most commonly due to a disorder of the thyroid gland (primary hypothyroidism), and it is accompanied by elevated TSH levels. In less than 5% of patients, hypothyroidism results from hypothalamic or pituitary disease (secondary hypothyroidism), in which case, low serum thyroid hormone levels are accompanied by inappropriately normal, or even low, serum TSH levels. Subclinical hypothyroid (SCH) refers to a state in which increased serum TSH levels are accompanied by normal serum levels of FT3 and FT4, in a patient who is generally asymptomatic.

Etiology

Hashimoto thyroiditis is the leading cause of hypothyroidism. Treatment of thyrotoxicosis with ^{131}I or thyroidectomy, drugs such as lithium, and iodine-containing drugs or contrast agents can also lead to primary hypothyroidism. Central hypothyroidism results from hypothalamic or pituitary diseases.

Epidemiology and Pathophysiology

Hypothyroidism is one of the most common endocrine disorders. Its prevalence increases with age, and it is much more common in women than in men. Up to 2% of women between 70 and 80 years of age have overt hypothyroidism. The prevalence of SCH in women older than 50 years of age is higher, between 5% and 10% [1]. Hashimoto thyroiditis is an autoimmune disorder due to lymphocytic infiltration of the thyroid gland with subsequent atrophy of its follicular cells and fibrosis. Between 50% and 80% of patients with SCH test positive for TPOAbs. Conversely, the presence of positive TPOAbs, even in clinically euthyroid patients with no previous history of hypothyroidism, suggests an increased risk of future development of overt hypothyroidism [13].

Diagnosis

An elevated serum TSH level is the most sensitive test to diagnose primary hypothyroidism.

Patients with "SCH" have normal serum FT4 and T3 concentrations and are usually asymptomatic, whereas those with overt disease typically have low serum thyroid hormone levels and nonspecific symptoms, such as cold intolerance, weight gain, constipation, dryness of the skin, fatigue, and periorbital edema. Population screening for subclinical thyroid disease has not been universally accepted because the benefits of subsequent therapy have not been clearly established in prospective clinical trials. In central hypothyroidism, low serum thyroid hormone levels are seen along with inappropriately normal or low serum TSH levels. Pituitary MRI is recommended to exclude the presence of pituitary or hypothalamic disease or tumors.

Treatment

Levothyroxine

LT4 is the treatment of choice for hypothyroidism. The usual replacement dose is 1.6 to 4.2 μg/kg/d and should be titrated to maintain serum TSH levels within normal range [51]. Serum TSH levels between 0.5 and 2.0 mIU/l are generally considered the optimal target [12]. Whether SCH should be treated remains controversial. Some studies suggest that early treatment may improve cardiac function, reverse mild symptoms of hypothyroidism and lower serum lipids [52,53], and improve memory [54], whereas others have shown no effect in total or low-density lipoprotein (LDL) cholesterol levels [55] or cognitive function [56].

LT4 plus Liothyronine (T3)

The use of combination LT4 and T3 in the treatment of hypothyroidism has been proposed as an alternative to LT4-only therapy, as a more physiologic form of thyroid hormone replacement [57]. Initial reports of improved mood and neuropsychological function with this combination [57] have not been confirmed by further controlled studies [58–61], despite patients' preference for this combination in some studies [62]. One study showed that combination therapy, when compared to LT4 alone, resulted in favorable changes in lipid profile but also in higher activation of bone resorption [61].

THYROID NODULES

Etiology

Autonomously functioning (toxic) adenomas may occur as the result of mutations in the TSHR or in the gene of the α-subunit of the G protein, leading to constitutive activation of the cAMP cascade and enhanced response to TSH. These mutations offer a growth and functional advantage to the cells affected, leading to development of an autonomously functioning nodule, inhibition of TSH secretion, and decreased

function of the rest of the gland. Toxic multinodular goiter results from gradual multiplication of autonomous follicles with varying degrees of function.

Epidemiology

Thyroid nodules are commonly seen in clinical practice. Their prevalence largely depends on the method of screening and the population evaluated. By palpation, the least sensitive method, their prevalence has been estimated around 4% [63]. Using high-resolution US, it has been reported to be as high as 68% [64,65]. Autopsy data from patients with no history of thyroid disease have indicated a prevalence of 50% [66]. Increasing age, female gender, iodine deficiency, and a history of head and neck irradiation seem to consistently increase the risk of developing thyroid nodules. The Framingham study estimated the annual incidence rate, by palpation, at 0.09% [63]. This means that in 2012, approximately 310,000 new nodules will be discovered in the United States. Many patients with a single palpable nodule have additional nodules when examined with US [67]. The prevalence of thyroid cancer is similar in patients with single or multiple nodules [68].

Diagnosis

Thyroid nodules are usually discovered by palpation of the neck during routine physical examination. Most clinically palpable thyroid nodules are at least 1 cm in diameter. Nodules can also be incidentally diagnosed during US of the neck done for unrelated conditions (so-called incidentalomas). TSH is the best test to determine whether a palpable nodule is hyperfunctioning. If so, TSH will be suppressed and confirmation with scintigraphy is recommended, because the likelihood of malignancy in such nodules is very small.

Fine needle aspiration (FNA) biopsy of thyroid nodules is the most important, cost-effective, and useful test in determining whether a nodule is benign or malignant. The mean sensitivity of FNA to detect thyroid cancer is 83% (65%–98%), its specificity 92% (72%–100%), and overall diagnostic accuracy 95% [69]. Its two major limitations are the inadequate or insufficient result and the suspicious or indeterminate cytologic findings, which occur in 15% and 20% of cases, respectively. Repeat US-guided biopsy may help overcome the first of these problems, but surgical excision is often needed to obtain a definitive diagnosis. Thyroid incidentalomas are very common. The incidence of cancer in such nodules ranges between 6% and 9% [21]. Prevalence of cancer was similar in nodules larger or smaller than 1 cm; irregular margins on US, microcalcifications, and intranodular vascular spots were independent predictors of malignancy, and 87% of cancers presented a solid hypoechoic appearance. FNA of nodules with at least one risk factor identified 87% of cancers [21,22].

Treatment

Surgery

All thyroid nodules confirmed to be malignant and most found suspicious by FNA biopsy should be referred for surgical excision [70,71]. The extent of the surgical procedure required is a matter of debate, with some authors advocating total or near-TT, and others favoring a more limited approach with lobectomy of the affected side. Benign thyroid nodules do not require surgery, unless they produce symptoms of compression or hyperthyroidism. Surgical excision is a reasonable option for patients with large or hyperfunctioning nodules, particularly if such nodules are associated with pressure symptoms [72].

Suppressive Therapy with Levothyroxine

Controversial evidence exists regarding the effectiveness of thyroid hormone suppressive therapy (THST) in reducing thyroid nodule size. One meta-analysis suggested an apparent therapeutic benefit of LT4 suppressive therapy in a subset

(20%–23%) of patients, with 1.9 to 2.5 times greater probability of achieving at least a 50% reduction in nodule size, when compared with placebo [73,74]. Another meta-analysis found no statistically significant effect [75]. Predictors of response have not been identified. Suppressive therapy is not indicated for hyperfunctioning nodules. A controlled trial of suppressive therapy in nontoxic multinodular goiters showed a better than 13% decrease in thyroid volume in 58% of patients treated with LT4 compared with only 5% of those given placebo [76]. However, another randomized study comparing LT4 therapy with RAI in patients with nontoxic multinodular failed to show a benefit of LT4 suppressive therapy with regard to goiter size reduction but showed significantly increased bone loss [77]. Routine T4 suppressive therapy for benign nodule is no longer recommended, and potential adverse effects on the cardiovascular and skeletal systems should always be considered [77,78].

Radioiodine Therapy

RAI is effective in reducing thyroid volume by up to 60% in patients with nontoxic multinodular goiter and improving compressive symptoms in most [79]. It is successful in the treatment of nearly 90% of single toxic adenomas, although the relatively high doses usually required result in long-term hypothyroidism in 10% to 20% of cases [72]. It is also 80% to 100% effective in the treatment of toxic multinodular goiter, although often several treatments may be necessary [80]. RAI therapy is also effective in patients with sporadic nontoxic goiters, resulting in volume reductions of up to 45% in 1 year [81]. Pretreatment with a single dose of rhTSH has been successfully used in Europe as adjuvant to RAI, improving the efficacy of RAI by enhancing uptake in nontoxic thyroid tissue and allowing the use of lower doses of RAI, while still resulting in greater reduction of goiter size [82]. rhTSH also potentiates the effect of RAI allowing a major reduction of the RAI activity without compromising its efficacy, but it increases fivefold the risk of posttherapy hypothyroidism [83]. Moreover, because the side effects are dose dependent, they are rare following doses of rhTSH of 0.1 mg or less [84].

Percutaneous Ethanol Injection

Percutaneous ethanol injection (PEI) should be reserved for patients who cannot, or will not, undergo standard therapy. Local pain, risk of recurrent laryngeal nerve damage, and the need for repeat treatments make PEI unsuitable for routine treatment of solid thyroid nodules. However, this procedure appears to be safe and effective in the treatment of predominantly cystic nodules, resulting in substantial reduction of nodule volume and amelioration of cosmetic and compressive symptoms in up to 80% of patients [85,86].

Laser Thermal Ablation (2B)

Ultrasound-guided laser thermal ablation (LTA) has emerged as an alternative therapeutic option in the management of patients with benign hypofunctioning thyroid nodules associated with compressive symptoms, who are poor surgical candidates or who refuse such intervention. This procedure has resulted in 45% to 60% reduction in nodule volume 6 months after treatment [87,88]. The procedure requires considerable skill of the operator and is currently performed only in a few specialized centers.

THYROID CANCER

Definition and Classification

Thyroid carcinomas are malignant neoplasms of the thyroid epithelium. Papillary and follicular cancers, collectively termed differentiated thyroid cancer, arise from the follicular epithelial cells. Other follicular cell–derived thyroid cancers (FDTC)

include the oxyphilic, or Hürthle cell variant, and the undifferentiated, anaplastic carcinoma. Medullary thyroid cancer (MTC) originates from the parafollicular, calcitonin-secreting cells (C cells). Papillary thyroid cancer (PTC) is the most common histologic type in the United States, accounting for 80% of thyroid cancers, followed by follicular thyroid carcinoma (FTC) with 10% to 15%, and MTC with about 5%. Of MTC patients, 75% have sporadic disease and 25% present with the hereditary or familial forms (MEN 2A, MEN 2B, and familial MTC).

Epidemiology

Thyroid cancer usually presents as a palpable nodule in the thyroid gland. Although thyroid nodules are very common, thyroid cancer is rare, constituting only 1% to 2% of all malignant neoplasms. It is three times more common in women than in men. Its annual incidence is approximately 0.5 to 10 per 100,000 in the world; some 40,000 new cases are diagnosed each year in the United States resulting in nearly 1,500 annual deaths [89]. Occult thyroid cancer, defined as any inapparent tumor found on a specimen by a pathologist, has been described in 0.5% to 13% of autopsy studies in the United States. Genetic (i.e., family history of thyroid cancer) or environmental factors (i.e., exposure to ionizing radiation) may be associated with the development of thyroid cancer in some populations. Nodule size larger than 4 cm, fixation to adjacent structures, enlarged regional LNs, vocal cord paralysis, rapid growth, and age younger than 15 years or older than 60 years predict a higher risk of malignancy.

Diagnosis

Fine-Needle Aspiration Biopsy

Most thyroid cancers present as a palpable thyroid nodule, often asymptomatic and are discovered during routine examination of the neck. FNA biopsy remains the single most accurate, reliable, and cost-effective test to diagnose thyroid cancer. Its sensitivity ranges between 65% and 98% (median 88%), specificity 72% to 100%, positive predictive value 46% to 100% (median 98%), negative predictive value 83% to 99% (median 97%), and its overall diagnostic accuracy is exceeds 95% [69,90]. The two major limitations of FNA are the inadequate or insufficient result, in 15% of cases, and the suspicious or indeterminate cytologic findings, seen in about 20% of satisfactory specimens. In the first case, repeat FNA, under US guidance, may increase the biopsy yield and provide an accurate diagnosis. However, specimens in which repeat aspiration fails to provide an adequate sample should be referred for excision, particularly if nodules are large, solid, or have other features suggestive of malignancy [71]. Suspicious nodules should be excised, given that the rate of malignancy in these nodules may be as high as 30% [69].

Thyroid Function Tests

All patients with a thyroid nodule should have serum TSH levels measured [71]. If high, TPOAbs should be obtained to exclude coexisting Hashimoto thyroiditis. Patients with low serum TSH and elevated FT4 levels may have a toxic nodule. Because the risk of malignancy in these hyperfunctioning nodules is low, a thyroid scan confirming the hyperfunctioning status may obviate the need for FNA [71].

Tumor Markers

Thyroglobulin, a glycoprotein produced in the thyroid gland in response to TSH stimulation, can only be reliably used as a tumor marker of differentiated thyroid cancer after total thyroid ablation, such as after thyroidectomy and ablative ^{131}I therapy. In these cases, serum Tg, in the absence of TgAb, is a reliable marker for the local recurrence of thyroid cancer, or for nodal or distant site metastasis. Sensitivity of Tg increases with TSH stimulation, either after T4 withdrawal or recombinant TSH (rTSH) administration, compared with during TSH suppression [17,91]. Tg measurement in needle washouts has been used to confirm

the presence of metastatic thyroid cancer after FNA biopsy of suspicious cervical lymph nodes (CLNs) in patients with a history of thyroid cancer [19,92]. It has been found to be more sensitive than FNA cytology of LNs and has the advantage of not being affected by the presence of anti-Tg antibodies in the serum [19,20,93].

Calcitonin, a product of the parafollicular C cells, is the most sensitive marker for the diagnosis and monitoring of MTC because most patients with MTC have elevated basal calcitonin levels and higher levels can be found even in subclinical disease. Injection of calcitonin secretagogues, such as calcium and pentagastrin (no longer available in the United States), result in increased serum calcitonin levels in patients with MTC, allowing for early detection of C-cell hyperplasia, even before the development of MTC. Provocative testing is now replaced with genetic testing for screening first-degree relatives of patients with MTC in the setting of familial MTC syndromes [94,95]. In the 5% of families with familial MTC but an undetected genetic mutation, screening for affected members should be done with calcitonin measurement after secretagogue administration. Peak values above 190 pg/ml for males and 130 pg/ml for females are abnormal. Mild elevations in basal or stimulated calcitonin levels should be interpreted with caution. Routine calcitonin measurement in the evaluation of patients with nodular thyroid disease (NTD) has been advocated by some authors in Europe [96], but this approach although reportedly cost effective [97] has not been adopted in the United States, because pentagastrin is no longer available in this country for confirmation of mildly abnormal results, leaving unresolved question about sensitivity and specificity [95].

Carcinoembryonic antigen (CEA) is a biochemical tumor marker of MTC. When used along with calcitonin, it is useful for monitoring MTC because persistent increase of these markers after curative surgery suggests residual or metastatic disease [95]. The levels seem to correlate with tumor burden, being higher in patients with clinically evident MTC than in occult disease.

Treatment

Surgery

Surgical excision of all tumor tissue in the neck is the primary therapy for patients with papillary and follicular thyroid cancer. The extent of the initial thyroid resection is still a matter of debate. No prospective controlled trials have been performed to settle this controversy. Although some authors argue that unilateral lobectomy is sufficient for most patients with PTC and FTC in the low-risk category, given the low cause-specific mortality and high complication rates with more extensive surgery [98], most clinicians [99–101] advocate total or near-TT because it decreases local recurrence, nodal metastases, and improves disease-free survival rates [99,101,102]. Unilateral lobectomy results in higher overall long-term recurrence rates (30% vs. 1% after TT followed by ^{131}I therapy). Papillary carcinomas are often multifocal and bilateral [103].

Near-TT facilitates ablation with ^{131}I and further follow-up with Tg and ^{131}I WBS to detect recurrent or metastatic disease. Lobectomy alone appears to be adequate surgery for small (<1 cm), unifocal, low-risk papillary microcarcinoma confined to the thyroid and without vascular invasion, in the absence of a history of head and neck irradiation [71,100].

TT with central neck dissection is recommended in all patients with biopsy-proven or suspected MTC because patients with familial MTC have bilateral multifocal disease and those with presumed sporadic disease represent the index case of familial MTC 10% to 20% of the time.

Radioiodine Remnant Ablation

Despite the widespread use of RAI in the postoperative treatment of patients with differentiated thyroid cancer, the indication for initial ablation and

subsequent ^{131}I diagnostic and therapeutic interventions remain controversial, due to lack of controlled, prospective studies. Some retrospective studies have shown decreased recurrence and disease-specific mortality with the early use of adjunctive ^{131}I therapy [100,104]. In a review of 1,599 patients followed at the M.D. Anderson Cancer Center, treatment with ^{131}I was the single most powerful prognostic indicator for disease-free interval and increased survival [99]. However, other studies show no such benefit, at least among most patients with PTC who are at low risk for mortality [105,106]. Patients with tumors greater than 1.5 cm and with residual disease after surgery are the ones more likely to benefit from RAI ablation. [104,105] Advantages of ^{131}I remnant ablation are:

- Elimination of residual uptake in the thyroid bed, facilitating ^{131}I concentration by cervical or pulmonary metastases
- Facilitating high TSH levels needed to enhance optimal tumor ^{131}I uptake
- Facilitate early detection of recurrence based on serum Tg measurement and /or RAI WBS
- Allowing use of Tg as reliable tumor marker in the absence of any residual normal thyroid tissue

^{131}I WBS is also used in the follow-up of thyroid cancer patients, to evaluate for the presence of residual or metastatic disease. Although therapeutic doses of ^{131}I have been standard of care in the treatment of recurrent or metastatic disease detected by diagnostic WBS, the benefit of treating Tg-positive, WBS-negative patients remains unclear. Such therapy may reduce tumor burden, but reduction in morbidity or mortality has not been demonstrated, and potential side effects may negate any benefit.

Thyroid Hormone Suppression of TSH

Decreased recurrence rates have been seen in thyroid cancer patients treated with LT4 as adjuvant therapy compared with findings in patients who did not receive such treatment [100,104,107]. In addition, one study found that constant TSH suppression to 0.05 mU/ml or less resulted in a longer relapse-free survival (RFS) than when TSH levels were 1 mU/ml or higher and that the degree of TSH suppression was an independent predictor of recurrence [108], and a meta-analysis demonstrated lower risk of adverse clinical outcomes (disease progression/recurrence/death) with the use of TSH suppressive therapy [109]. However, no controlled study has yet determined the optimal level of TSH suppression that would result in maximal survival benefit while minimizing potential adverse effects of prolonged suppressive therapy.

Tyrosine Kinase Inhibitors

In many cases, advanced metastatic differentiated thyroid cancer that is refractory to conventional treatment modalities such as surgery, RAI, and external beam radiation therapy may respond to a new class of drugs known as tyrosine kinase inhibitors (TKIs) [110], and these drugs have also been used with some success in arresting the growth and progression of metastatic hereditary MTC [111].

EUTHYROID SICK SYNDROME

Definition and Etiology

The term euthyroid sick syndrome (ESS) refers to abnormalities in thyroid function tests seen in patients with serious systemic nonthyroidal illnesses, which are often the result of variable disturbances in the hypothalamic–pituitary–thyroid axis, thyroid hormone binding to serum proteins, tissue uptake, or thyroid hormone metabolism [112]. The most common abnormalities include low serum T3 and increased reverse T3 levels, and with more severe and prolonged illness, T4

levels also decrease, portending a worse prognosis. TSH levels are usually normal but may be mildly or frankly suppressed.

Pathophysiology

Although the mechanisms of the abnormalities found in ESS are not clear, several pathogenic factors have been implicated, including decreased peripheral T4 to T3 conversion, abnormalities in serum thyroid binding proteins, decreased TRH response and TSH release, low tissue uptake, altered metabolism of thyroid hormones, and increased levels of cytokines.

Diagnosis

Exclusion of thyroid disease in acutely ill patients may be challenging. Nonthyroidal illnesses may present with a spectrum of thyroid function abnormalities, commonly seen in patients with intrinsic thyroid pathology. Low serum T3 levels with normal T4 and TSH levels is the most common finding in ESS. Serum TSH levels are typically normal or mildly reduced in 80% of patients. A previous history of thyroid disease, external irradiation, presence of a goiter, or midline neck scar may point to a true primary thyroid condition. In general, it is best not to rely on any single thyroid function test in the setting of nonthyroidal illnesses [112] and to wait until after recovery from nonthyroidal illnesses before evaluating thyroidal status. TSH testing in hospitalized patients may be fairly inaccurate, resulting in low yield of true-positive and many false-positive results [3]. A study of 1,580 medical inpatients, evaluated with TSH on admission, found a 17% rate of abnormal levels; after following 63% of those with abnormal results and retesting after resolution of illness, 85% were found to be euthyroid [10]. False-positive results are usually due to acute nonthyroidal illnesses and drug interactions, especially glucocorticoids.

Treatment

Triiodothyronine Replacement

Given the increased mortality seen in patients with severe nonthyroidal illnesses and low T4 values [113], some studies have evaluated the effect of thyroid hormone therapy in such patients. A controlled study showed that T3 administration to patients undergoing coronary bypass procedures improves cardiac hemodynamics as well as decreases postoperative ischemia, inotropic requirements, mortality rate, and length of hospital stay [114]. Other studies failed to confirm these benefits [115,116].

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Evaluation of Thyroid Function

Thyroid-Stimulating Hormone

1. (1C) **Helfand M, Redfern CC.** Screening for thyroid disease: An update. Clinical guideline, Part 2. Ann Intern Med 1998;129:144–158.

   This study evaluated the benefits of screening asymptomatic patients for thyroid dysfunction with a sensitive TSH test and to evaluate the efficacy of treatment for subclinical thyroid dysfunction in the general adult population. Thirty-three studies of screening and twenty-three controlled studies on treatment of subclinical thyroid dysfunction were included. Screening can detect symptomatic, unsuspected, overt thyroid dysfunction, with highest yield in women older than 50 years of age. In this group, 1 in 71 women screened could benefit from relief of symptoms. Evidence of the efficacy of treatment for subclinical thyroid dysfunction is inconclusive.

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   This cost-utility analysis was undertaken to estimate cost-effectiveness of periodic screening for mild thyroid failure by measuring serum TSH levels in hypothetical cohorts of women

and men screened every 5 years during the periodic examination, beginning at age 35 years. The cost-effectiveness of screening 35-year-old patients with a serum TSH every 5 years was $9,223 per quality-adjusted life years (QALYs) for women and $22,595 per QALY for men; it improved when age at first screening was increased for both genders and was always more favorable for women. Reduced progression to overt hypothyroidism and relief of symptoms increased QALYs, but they did not reduce direct medical costs. The cost-effectiveness of screening for mild hypothyroidism compares favorably with other accepted preventive medical practices.

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   A systematic review of the literature from 1966 to 1996 was undertaken to estimate the prevalence of undiagnosed thyroid disease, review the usefulness of clinical signs and symptoms, and elucidate characteristics of sensitive TSH testing among inpatients. Results indicated that the prevalence of thyroid disease among inpatients is 1% to 2%, similar to the outpatient population. Absence of clinical features of thyroid disease lowers the pretest likelihood and makes screening even less useful. Presence of clinical features specific for thyroid disease may increase pretest likelihood and yield of testing. Acute illness reduces the specificity of sensitive TSH tests. The positive likelihood ratio of an abnormal TSH result in ill inpatients is about 10 compared with about 100 in outpatients.

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   This comprehensive review describes the debate and controversy currently surrounding the recommendations of a consensus conference that considered issues related to the management of early, mild, or so-called subclinical hypothyroidism and hyperthyroidism and the controversies surrounding the definition of the normal reference range for TSH. The development of more highly sensitive TSH assays coupled with the appreciation that reference populations previously considered normal were contaminated with individuals with various degrees of thyroid dysfunction resulting in increased mean TSH levels for the group. The article discusses laboratory guidelines from the National Academy of Clinical Biochemistry which indicate that more than 95% of normal individuals have TSH levels below 2.5 mU/l.

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   This article reports an analysis of TSH distribution in a subset (766 of 1,861 patients) of the Hanford Thyroid Disease Study cohort, which included a population with no evidence of thyroid disease, thyroid autoantibodies, no history of thyroid medications, and a normal thyroid ultrasound. The shape of the TSH distribution was compared with the Gaussian and lognormal distributions. The TSH distribution in the subset of patients was right skewed and followed an approximate lognormal distribution. The best estimates of the 97.5th percentile, the percentage above 2.5 μIU/ml, and the percentage above 3.0 μIU/ml for TSH by third generation immunochemiluminometric assay are 4.1 μIU/ml, 20% and 10.2%, respectively, indicating that the TSH reference range should be narrowed, supporting a value of approximately 4.0 as the upper reference limit.

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   This study reviews data from the Reference Group of NHANES III, 14,333 people without known thyroid disease or TPO antibodies; 85% had TSH levels below 2.5 mIU/l and 2.3% had SCH. An additional 9.7% had upper reference range (URR) TSH (values between 2.5 and 4.5 mIU/l), representing 20.6 million Americans, who would also be identified as SCH if the upper TSH limit were decreased.

   It also describes some of the pitfalls of TSH testing including its variability depending on time of phlebotomy and other factors that may affect serum TSH levels. Although about half of those with URR TSH probably have thyroid disease, most with thyroid disease, TPOAbs, have TSH below 2.5 mIU/l. Those with URR TSH with thyroid disease probably have minimal thyroid deficiency, without any reported adverse health consequences or benefit of treatments with LT4. It concludes that because routine LT4 treatment is not recommended for SCH, it is certainly not warranted in individuals with URR TSH. However, it recommends serum TSH measurement every 1 to 2 years in these patients.

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   The authors analyzed TSH, antithyroid antibodies, and TSH frequency distribution curves for specific age deciles in populations without thyroid disease, with or without antithyroid antibodies. Among those without thyroid disease, 10.6% of 20- to 29-year-olds had TSH greater than 2.5 mIU/l, increasing to 40% in the 80+ group, 14.5% of whom had TSH greater than 4.5 mIU/l.

When TSH was greater than 4.5 mIU/l, 67.4% in the age 40- to 49-year group and 40.5% in the 80+ group had antibodies. TSH frequency distribution curves of the 80+ group were displaced to higher TSH. The 97.5 percentiles for the 20 to 29 and 80+ groups were 3.56 and 7.49 mIU/l, respectively, and 70% of older patients with TSH greater than 4.5 mIU/l were within their age-specific reference range. The study confirms that TSH distribution progressively shifts toward higher concentrations with age and points out that the prevalence of SCH may be significantly overestimated unless an age-specific range for TSH is used.

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Free T4 and Free T3

11. (4) **Stockigt JR.** Free thyroid hormone measurement: A critical appraisal. Endocrinol Metab Clin North Am 2001;30:265–289.

    This article reviews the advantages of free thyroid hormone determination, changes in binding proteins that may result in abnormal total thyroid hormone levels, and their underlying causes; describes available assays to determine free thyroid hormone levels, advantages and limitations of each, and circumstances in which FT4 levels may be affected requiring cautious interpretation.

12. (4) **Demers LM, Spencer CA.** Laboratory medicine practice guidelines: Laboratory support for the diagnosis and monitoring of thyroid disease. Clin Endocrinol 2003;58:138–140.

    Excellent detailed review on clinical usefulness, methodology, pitfalls, and recommendations on the use of all available tests of thyroid function for the practicing clinician and bioanalyst.

Thyroid Autoantibodies

13. **Walsh,** et al. Thyrotropin and thyroid antibodies as predictors of hypothyroidism: A 13-year, longitudinal study of a community-based cohort using current immunoassay techniques. J Clin Endocrinol Metabol 2010;95:1095–1104.

    This prospective, longitudinal study on the predictive value of thyroid antibodies evaluated 1,184 participants in the 1981 and 1994 Busselton Health Survey, measuring TSH, free T(4), TPOAbs, and Tg Abs. This cohort was subsequently assessed at follow-up 13 years later for development of mild (TSH > 4.0 mU/l) or overt hypothyroidism (TSH > 10.0 mU/l). At 13-year follow-up, 110 subjects had hypothyroidism, of whom 42 had overt hypothyroidism. TSH cut-

offs of 2.5 and 4.0 mU/l, combined with TPOAbs, provide a clinically useful estimate of the long-term risk of hypothyroidism.

14. (2) **Feldt-Rasmussen U,** et al. Meta-analysis evaluation of the impact of thyrotropin receptor antibodies on long term remission after medical therapy of Graves disease. J Clin Endocrinol Metab 1994;78:98–102.

    This meta-analysis reviewed the evidence of 10 prospective and 8 retrospective studies including a total of 1,524 patients. The prospective studies demonstrated a 65% risk reduction (RR) in relapse in TRAb-negative patients compared with those with positive antibodies after antithyroid drug therapy. An even greater RR (92%) was seen in retrospective studies. Overall RR was 78% (all studies).

15. (2) **Matsura N,** et al. TSH-receptor antibodies in mothers with Graves' disease and outcome in their offspring. Lancet 1988;1:14–17.

    Blood was taken from 56 selected newborn babies whose mothers had Graves disease to assess the relationship between their thyroid function and the presence of TSH-binding inhibitor immunoglobulins (TBIIs) and TSAbs in maternal serum. All the mothers of these thyrotoxic babies had both antibodies in their serum. Most of the mothers whose thyroid function had been well controlled in pregnancy gave birth to unaffected babies. Fifteen babies had a transient syndrome of low serum T4 and FT4 with normal TSH levels, which tended to be associated with TRAbs in maternal serum (TBII 9/15, TSAb 4/15). Two infants had transient hyperthyroxinemia without hyperthyroidism, and both their mothers showed strong TSAb activity without TBII activity.

16. (2) **Spencer CA,** et al. Serum thyroglobulin autoantibodies: Prevalence, influence on serum thyroglobulin measurement, and prognostic significance in patients with differentiated thyroid carcinoma. J Clin Endocrinol Metab 1998;83:1121–1127.

    This case-control study investigated the prevalence of TgAb in a normal and differentiated thyroid cancer patient population and the influence of TgAb on serum Tg measurement in 4,453 healthy control subjects and 213 patients with differentiated thyroid cancer. TgAbs and TPOAbs were measured in all differentiated thyroid cancer patients and controls. Serum Tg and TgAb levels were measured in 15 TgAb-negative sera and in 97 TgAb-positive sera. The prevalence of thyroid autoantibodies was increased threefold in patients with differentiated thyroid cancer compared with the general population (40% vs. 14%). Serum TgAb was present in 25% of differentiated thyroid cancer patients and 10% of controls. Serial postsurgical serum TgAb and Tg patterns correlated with presence or absence of disease. TgAb interference was found in 69% of TgAb-positive sera and was more frequent and severe in sera containing high TgAb levels.

Thyroglobulin

17. (4) **Spencer CA, Wang CC.** Thyroglobulin measurement: Technique, clinical benefits, and pitfalls. Endocrinol Metab Clin North Am 1995;24:841–863.

    This article reviews in detail advantages, clinical usefulness, and potential pitfalls of Tg measurement, as a serum marker in the management of patients with thyroid cancer.

18. (1) **Haugen BR,** et al. A comparison of recombinant human thyrotropin and thyroid hormone withdrawal for the detection of thyroid remnant or cancer. J Clin Endocrinol Metab 1999;84:3877–3885.

    This randomized clinical trial compared the effect of rTSH with thyroid hormone withdrawal on the results of ^{131}I WBS and serum Tg levels in 229 adult patients with differentiated thyroid cancer requiring ^{131}I WBS. Patients received 0.9 mg rTSH every 24 hours for two doses (arm I) or every 72 hours for three doses (arm II). Twenty-four hours after the second or third dose, respectively, 4 mCi ^{131}I was given and a WBS obtained 48 hours later. At least 2 weeks after the second or third dose, patients were withdrawn from LT4, and when TSH was over 25 mU/l, 4 mCi ^{131}I was administered and WBS performed 48 hours later. ^{131}I WBS results were concordant between the rTSH-stimulated and LT4 withdrawal phases in 89% of patients. Of the discordant scans, 4% of results were superior after rTSH administration and 8% after LT4 withdrawal. Based on a serum Tg level above 2 ng/ml, thyroid tissue or cancer was detected during LT4 therapy in 22%; after rTSH stimulation in 52%; and after LT4 withdrawal in 56% of patients with disease or tissue limited to the thyroid bed, and in 80%, 100%, and 100% of patients, respectively, with metastatic disease. Combination of ^{131}I WBS and serum Tg after rTSH stimulation detected thyroid tissue or cancer in 93% of patients with disease or tissue limited to the thyroid bed, and in 100% of those with metastatic disease.

19. (2) **Baskin HJ.** Detection of recurrent papillary thyroid carcinoma by thyroglobulin assessment in the needle washout after fine-needle aspiration of suspicious lymph nodes. Thyroid 2004;14:959–963.

    In this prospective study, US was performed on 74 postoperative patients being followed for stage I and II papillary carcinoma. All patients were clinically free of cancer 1 to 43 years after a

TT, and were screened with US and Tg measurement while taking thyroid hormone suppression. Twenty-one patients with sonographic findings suspicious of recurrent disease in the LNs of the neck underwent US-guided FNA for cytology and Tg analysis, and seven of these patients tested positive for Tg in their needle washout. Only three of them had detectable Tg in their serum, and only five of the seven had positive cytology. The author proposes US with FNA-Tg analysis of needle washout of suspicious LNs as an effective and efficient method of surveillance in low-risk patients. Presence of Tg in the needle washout proved to be more sensitive than cytology in diagnosing cancer in the LNs and was not affected by positive anti-Tg antibodies in the serum.

20. **Cunha,** et al. Thyroglobulin detection in fine-needle aspirates of cervical lymph nodes: a technique for the diagnosis of metastatic differentiated thyroid cancer. Eur J Endocrinol 2007;157:101–107.

    This study evaluated the utility of Tg measurement in FNA-Tg for detecting CLN metastases from FDTC. Sixty-seven patients with eighty-three suspicious CLNs underwent US-FNA for cytology and Tg measurement in the needle washout. Measurement of anti-Tg antibodies (FNA-TgAb) was also carried out in half of all the aspirates.

    Subjects were divided into two groups: 1 of 16 patients awaiting thyroidectomy and the other of 51 patients in follow-up after surgery. The first group of patients had positive FNA biopsy (FNAB-Tg) in 14 of 18 studied CLNs, while FNAB cytology indicated metastasis in only 8 out of the 14 CLNs with positive histology. A total of 65 CLNs were studied in the follow-up group. Lymphadenectomy was performed in 23 patients, and 28 aspirated CLNs were removed. Histology confirmed the diagnosis of metastasis suggested by FNAB-Tg in 20 CLNs and of reactive lymphadenitis in the remaining 8 CLNs while FNAB cytology was positive in only 11 CLNs. Sensitivity of FNAB-Tg was 100% in both groups and was not affected by the presence of TgAb.

Thyroid Imaging

Ultrasound

21. (2) **Papini E,** et al. Risk of malignancy in nonpalpable thyroid nodules: Predictive value of ultrasound and color Doppler features. J Clin Endocrinol Metab 2002;87:1941–1946.

    This study evaluated 494 patients with nonpalpable hypofunctioning thyroid nodules, identified by US and color Doppler, in clinically euthyroid subjects, over a 5-year period. All patients had FNA biopsy of the nodules. Patients with suspicious or malignant cytology underwent surgery. Thyroid cancer was found in 9% of solitary nodules and 6% of multinodular goiters, and its prevalence was similar in nodules both larger and smaller than 10 mm (9% vs. 7%). At US, 87% of cancers presented a solid hypoechoic appearance. Irregular margins (RR, 16.83), intranodular vascular spots (RR, 14.29), and microcalcifications (RR, 4.97) were independent predictors of malignancy. FNA of hypoechoic nodules with at least one risk factor identified 87% of cancers.

22. (4) **Fish,** et al. Sonographic imaging of thyroid nodules and cervical lymph nodes. Endocrinol Metab Clin North Am 2008;37:401–417.

    This article discusses the sonographic features of thyroid nodules associated with malignancy and the role of ultrasound in the management of patients with thyroid cancer.

23. (2) **Frasoldati A,** et al. Diagnosis of neck recurrences in patients with differentiated thyroid carcinoma. Cancer 2003;97:90–96.

    In this cohort study, the authors compare the sensitivity of Tg measurement after LT4 withdrawal, ^{131}I WBS, and US in the diagnosis of differentiated thyroid carcinoma (DTC) neck recurrences in 494 DTC patients, after TT and subsequent radioablative ^{131}I treatment. Mean follow-up time was 55.1 ± 37.7 months. Neck DTC recurrences were detected in 51 (10.3%) patients and occurred after 44.6 ± 21.4 months from initial treatment. Serum Tg levels increased (≥2 ng/ml) off LT4 therapy in 29 patients (sensitivity 56.8%), ^{131}I WBS showed neck uptake in 23 patients (sensitivity 45.1%), coexisting distant metastases were detected in 9 of 23 patients, and US identified neck recurrence in 48 patients (sensitivity 94.1%). Neck US is more sensitive than traditional techniques for surveillance of DTC patients, detecting recurrences even in patients with undetectable serum Tg levels and negative WBS and is recommended as the first-line test in the follow-up of all DTC patients.

Scintigraphy

24. (4) **Meier DA, Kaplan MM.** Radioiodine uptake and thyroid scintiscanning. Endocrinol Metab Clin North Am 2001;30:291–313.

    This article reviews current uses of radioactive iodine uptake (RAIU) testing and radionuclide thyroid scanning in thyroid conditions other than thyroid cancer.

25. (2) **Gallowitsch HJ,** et al. Thyroglobulin and low-dose iodine-131 and technetium-99m tetrosfosmin whole-body scintigraphy in differentiated thyroid carcinoma. J Nucl Med 1998;39:870–875

This study was undertaken to compare low-dose ^{131}I scan and 99mTc-WBS, using Tg-off-LT4 as a basis for comparison in 58 patients with differentiated thyroid cancer ablated with thyroidectomy and ^{131}I therapy. ^{131}I revealed 19 of 44 tumor sites and 3 remnants. Sensitivity showed decreasing values for local recurrences (57%), bone (54%), mediastinal (50%), lung (43%), and LN (22%) metastases. Moreover, 99mTc-WBS revealed a total of 39 of 44 malignant lesions (89%). Sensitivity was superior for lung (100%), mediastinal (100%), and LN metastases (90%) and inferior for bone metastases (85%). Local recurrences were detected in 86% of patients, and thyroid remnants in 18%. Tg-off-LT4 detected malignant recurrence or metastases in 95% of patients when a cutoff of 3 ng/ml was used, and in 84% using a cutoff of 10 ng/ml. Specificity was 72% for a cutoff of 0.5 ng/ml, 90% for cutoff of 3 ng/ml, and 100% if a cutoff of 10 ng/ml was used.

26. (4) **Haugen BR, Lin EC.** Isotope imaging for metastatic thyroid cancer. Endocrinol Metab Clin North Am 2001;30:469–492.

    This excellent article provides a review of all different isotope imaging modalities currently available for the evaluation of metastatic thyroid cancer, with indications, advantages, and weaknesses of each modality and provides a suggested algorithm for imaging patients with suspected thyroid cancer recurrence or metastases.

27. **Basaria M,** et al. The use of recombinant thyrotropin in the follow-up of patients with differentiated thyroid cancer. Am J Med 2002;112:721–725.

    This article reviews the utility, diagnostic advantages, and possible adverse effects of the use of rhTSH in the evaluation and management of patients who require RAI scanning for routine follow-up in comparison with the more traditional alternative of thyroid hormone withdrawal. The combination of a WBS and a serum Tg measurement can identify virtually all patients with distant metastatic disease. A serum Tg greater than 2 ng/ml and/or a positive WBS after rhTSH stimulation suggest residual thyroid tissue or neoplastic disease. The use of rhTSH, although expensive, has fewer adverse effects than withdrawal of thyroid hormone replacement, although nausea and headache have been reported.

28. (2) **Robbins RJ,** et al. Preparation by recombinant human thyrotropin or thyroid hormone withdrawal are comparable for the detection of residual differentiated thyroid carcinoma. J Clin Endocrinol Metabol 2001;86:619–625.

    This is a retrospective analysis of a cohort of patients undergoing routine follow-up testing to detect recurrent thyroid carcinoma over a 2-year period. One group was prepared for testing by thyroid hormone withdrawal (THW), and the other group remained on thyroid hormone and received injections of rhTSH before diagnostic WBS (DxWBS). Two hundred eighty-nine patients were examined both by DxWBS and by measurement of the serum Tg response to elevated TSH levels. THW was used for 161 patients, and rhTSH preparation was used for 128 patients. Based on all available testing results, patients were classified as having metastatic disease, thyroid bed uptake only, or no evidence of disease. The sensitivity and specificity of the two tests were comparable between groups. No significant differences were present in the positive or negative predictive values between groups. The highest negative predictive value (97%) was in patients who had both a negative DxWBS and low stimulated Tg levels after rhTSH. In summary, the study showed that preparing patients by rhTSH is diagnostically equivalent to preparing them by THW.

Positron Emission Tomography with ^{18}F-Fluorodeoxyglucose

29. (2) **Hooft L,** et al. Diagnostic accuracy of ^{18}F-fluorodeoxyglucose positron emission tomography in the follow-up of papillary or follicular thyroid cancer. J Clin Endocrinol Metab 2001;86:3779–3786.

    Systematic review to determine the diagnostic accuracy of positron emission tomography with 18-fluorodeoxyglucose (FDG-PET) in patients suspected of recurrent differentiated thyroid cancer. Fourteen studies with 10 or more subjects, evaluating the accuracy of FDG-PET in differentiated thyroid cancer, were included. All studies claimed a positive role for PET, but at evidence levels 3 or 4 (lowest), precluding quantitative analysis. Methodologic problems included poor validity of reference tests and lack of blinding of test performance and interpretation. The material was heterogeneous with respect to patient variation and validation methodology. The most consistent data were found on the ability of FDG-PET to provide an anatomical substrate in patients with elevated serum Tg and negative ^{131}I scans.

30. (2) **Chung JK,** Lee JS. Value of FDG PET in papillary thyroid carcinoma with negative ^{131}I whole-body scan. J Nucl Med 1999;40:986–992.

    This prospective study evaluated the utility of FDG-PET in localizing metastatic disease in 54 athyrotic PTC patients (33 with metastatic tumors and 21 patients in remission) with negative diagnostic ^{131}I WBS. FDG-PET revealed metastases in 31 patients (sensitivity 94%), but Tg levels were elevated only in 18 (sensitivity 55%). PET results were positive in 14 of 15 metastatic patients with normal Tg levels. PET results were negative in 20 patients with disease

in remission (specificity 95%), whereas Tg levels were normal in 16 patients (specificity 76%). In patients with normal ^{131}I scans, PET detected metastases in CLNs in 88%, lung in 27%, mediastinum in 33%, and bone in 9%. In contrast, among 117 patients with ^{131}I scan–positive functional metastases, ^{131}I scan detected metastases in CLNs in 62%, lung in 56%, mediastinum in 22%, and bone in 16%. PET showed increased uptake in cervical or mediastinal LNs in all patients with false-negative Tg results. Metastasis was confirmed in all (11) patients with increased FDG uptake in CLNs.

31. (2) **Grunwald F** et al. Fluorine-18 fluorodeoxyglucose positron emission tomography in thyroid cancer: results of a multicentre study. Eur J Nucl Med 1999;26:1547–1552.

    This study evaluates the clinical significance of 18F-FDG-PET in DTC comparing the results with both ^{131}I WBS and 99mTc2-methoxyisobutylisonitrile (MIBI). Whole-body PET imaging using FDG was performed in 222 patients: 134 with papillary tumors, 80 with follicular tumors, and 8 with mixed cell–type tumors. Finally, clinical evaluation was done including histology, cytology, Tg level, US, CT, and subsequent clinical course to allow comparison with functional imaging results. Sensitivity of FDG-PET was 75% and 85% for the whole patient group and the group with negative^{131}I WBS, respectively. Specificity was 90% in the whole patient group. Sensitivity and specificity of WBS were 50% and 99%, respectively. When results of FDG-PET and WBS were considered in combination, tumor tissue was missed in only 7%.

32. (2) **Dong MJ,** et al. Value of ^{18}F-FDG-PET/PET-CT in differentiated thyroid carcinoma with radioiodine-negative whole-body scan: A meta-analysis. Nuc Med Commun 2009;30:639–650.

    This article evaluated the diagnostic accuracy of ^{18}F-FDG-PET and FDG-PET/CT in the detection of recurrent or metastatic DTC not identified by RAI WBS. The authors reviewed a total of 25 studies (comprising 789 patients) that were published from January 1990 to September 2008. Systematic methods were used to identify, select, and evaluate the methodologic quality of the studies and to summarize the overall findings of sensitivity and specificity. In total, 17 studies with 571 patients who had recurrent or metastatic DTC and negative WBS were collected, and the overall patient-based sensitivity and specificity of FDG-PET were 0.835 (95% confidence interval [CI], 0.791–0.873) and 0.843 (95% CI, 0.791–0.886), respectively. The pooled sensitivity and specificity in the DTC patients who presented with elevated serum Tg and negative ^{131}I scan were 88.5% and 84.7%, respectively. In six studies where the 165 patients were diagnosed by using FDG-PET/CT, pooled sensitivity and specificity were 93.5% and 83.9%, respectively. FDG-PET is especially effective in detecting patients with elevated Tg levels and normal ^{131}I WBS while FDG-PET/CT is more sensitive in the follow-up of thyroid cancer recurrence or metastases, particularly in those with negative WBS.

Hyperthyroidism

33. (4) **Weetman AP.** Graves' disease. N Engl J Med 2000;343:1236–1248.

    This excellent review covers the pathogenesis of Graves disease, predisposing genetic and environmental factors, epidemiology, clinical manifestations, diagnosis, natural history, therapeutic options, management during pregnancy, and treatment of ophthalmopathy.

34. **Russo D,** et al. Genetic alterations in thyroid hyperfunctioning adenomas. J Clin Endocrinol Metab 1995;80:1347–1351.

    Thirty-seven thyroid autonomously hyperfunctioning adenomas were screened for mutations in the TSHR, G alpha s (gsp), and ras genes. Polymerase chain reaction-amplified fragments of the TSHR C-terminal part (exon 10), gsp (exons 8 and 9), and the three ras genes were obtained from the genomic DNA extracted from 37 tumors and their adjacent normal tissues and were studied by direct nucleotide sequencing and hybridization with synthetic probes. A point mutation in the third intracellular loop (codon 623) of the TSHR was found in 3 of 37 (10%) adenomas studied. This mutation codes for a change in the TSHR structure and is somatic and heterozygotic. Constitutive activation of the TSHR was demonstrated by an increase in basal cAMP levels after transfection of CHO cells with a mutated Ser 623-TSHR complementary DNA. Nine gsp- and one ras-activating mutations were also detected. No simultaneous alteration of the studied genes was present.

Antithyroid Drugs

35. (1) **Reinwein D,** et al. A prospective randomized trial of antithyroid drug dose in Graves' disease therapy. J Clin Endocrinol Metab 1993;76:1516–1521.

    This prospective, randomized, multicenter trial evaluated whether higher doses of methimazole result in higher long-term remission rates of hyperthyroidism in Graves disease in 309 patients with Graves disease from 18 thyroid clinics in Europe. Patients were given methimazole, 10 or 40 mg, with LT4 for 1 year, and 1 year of follow-up. Both doses were equally effective in achieving remission, although euthyroidism was achieved 3 weeks at higher dosages. There was no difference in relapse rates between the two groups (36% vs. 37%) or in length of time

between stopping treatment and relapse, but the rate of adverse reactions was significantly higher in the 40-mg group (26% vs. 15%).

36. (3) **Rivkees SA, Szarfman A.** Dissimilar hepatotoxicity profiles of propylthiouracil and methimazole in children. J Clin Endocrinol Metabol 2010;95:3260–3267.

    The objective of this study was to assess safety and hepatotoxicity profiles of PTU and methimazole by age in the U.S. FDA's Adverse Event Reporting System (AERS).

    The authors used the multi-item gamma-Poisson shrinker (MGPS) data mining algorithm to analyze more than 40 years of safety data in AERS, to calculate adjusted observed to expected ratios (empiric Bayes geometric mean [EBGM] values) focusing on hepatotoxicity events.

    MGPS identified higher-than-expected reporting of severe liver injury in pediatric patients treated with PTU but not with methimazole. PTU had a high adjusted reporting ratio for severe liver injury (EBGM 17; 90% CI: 11.5–24.1) in the group less than 17 years old. The highest EBGM values for methimazole were with mild liver injury in the group 61 years and older (EBGM 4.8 [3.3–6.8]), which consisted of cholestasis. Vasculitis was also observed for PTU in children and adolescents, reaching higher EBGM values than hepatotoxicity signals.

37. (1) **Bahn RS,** et al. Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. Endocr Pract 2011;17(3):456–520.

    This article describes evidence-based clinical guidelines for the management of thyrotoxicosis that would be useful to generalist and subspecialty physicians and others providing care for patients with this condition. The American Thyroid Association (ATA) and American Association of Clinical Endocrinologists (AACE) assembled a task force of expert clinicians who examined relevant literature using a systematic PubMed search supplemented with additional published materials. An evidence-based medicine approach that incorporated the knowledge and experience of the panel was used to develop the text and a series of specific recommendations. The strength of the recommendations and the quality of evidence supporting each was rated according to the approach recommended by the Grading of Recommendations, Assessment, Development, and Evaluation Group. One hundred evidence-based recommendations were developed to aid in the care of patients with thyrotoxicosis and to share what the task force believes is current, rational, and optimal medical practice.

38. (1) **Allannic H,** et al. Antithyroid drugs and Graves' disease: A prospective randomized evaluation of the efficacy of treatment duration. J Clin Endocrinol Metab 1990;70:675–679.

    This prospective, randomized clinical trial compared the efficacy of 18 months versus 6 months of ATD therapy on remission rates of Graves hyperthyroidism in 94 patients with Graves disease. Carbimazole was given in doses needed to maintain clinical euthyroidism for 6 months (group 1) or 18 months (group 2). Treatment for 18 months resulted in higher remission rates 2 years after discontinuation of treatment (62% vs. 42%; $p = 0.05$).

39. (1) **Abraham,** et al. A systematic review of drug therapy for Graves' hyperthyroidism. Eur J Endocrinol 2005;153:489–498.

    This is a systematic review and meta-analyses of randomized controlled trials (RCTs) evaluating the effects of dose, regimen, and duration of antithyroid drug therapy for Graves thyrotoxicosis on recurrence of hyperthyroidism, course of ophthalmopathy, adverse effects, health-related quality of life, and economic outcomes. Six databases and trial registries were searched. Trials included provided therapy for at least 6 months with follow-up at least 1 year after drug cessation. Fixed or random effects meta-analyses were used to combine study data. Twelve trials compared a block-replace regimen with a titration regimen. Overall, there was no significant difference between the regimens for relapse of hyperthyroidism. Participants were more likely to withdraw due to adverse events with a block-replace regimen (RR = 1.89, 95% CI, 1.25–2.85). Prescribing replacement thyroxine, either with the antithyroid drug treatment or after this was completed, had no significant effect on relapse. Limited evidence suggested that 12 to 18 months of antithyroid drug treatment should be used. The titration regimen appeared as effective as the block-replace regimen but had fewer adverse effects. However, relapse rates over 50% and high participant dropout rates in trials mean that the results should be interpreted with caution. There were no data on the course of ophthalmopathy, health-related quality of life, and economic outcomes.

40. (1) **Maugendre D,** et al. Antithyroid drugs and Graves' disease-prospective randomized assessment of long-term treatment. Clin Endocrinol 1999;50:127–132.

    This prospective, randomized trial was undertaken to determine benefits of a 42-month compared with an 18-month treatment with carbimazole. The population comprised 142 patients with Graves disease who were given carbimazole at doses needed to achieve euthyroidism for 18 months (group 1) or 42 months (group 2). There was no difference in relapse rate between the two groups (36% vs. 29%, NS), or in percentage of TPOAb-positive patients

(53% vs. 46%; p = NS). The percentage of patients with TSAb was lower in group 2 (18% vs. 42%; $p = 0.004$) at treatment withdrawal.

41. (1) **Azizi F,** et al. Effect of long-term continuous methimazole treatment of hyperthyroidism: Comparison with radioiodine. Eur J Endocrinol 2005;152:695–701.

In this prospective, randomized study, the authors investigate the long-term effects of continuous methimazole (MMI) therapy in 104 patients whose hyperthyroidism recurred within 1 year after discontinuing 18 months of MMI treatment. They were randomized into two groups for continuous ATD and RAI treatment. Numbers of occurrences of thyroid dysfunction and total costs of management were assessed during 10 years of follow-up. At the end of the study, 26 patients were still on continuous MMI (group 1), and of 41 ^{131}I-treated patients (group 2), 16 were euthyroid and 25 became hypothyroid. There was no significant difference in age, sex, duration of symptoms, and thyroid function between the two groups. No serious complications occurred in any of the patients. The cost of treatment was lower in group 1. At the end of 10 years, goiter rate was greater and TPOAb concentration was higher (RR 1.8) in group 1 than in group 2. Serum total and LDL cholesterol concentrations were higher (RR 1.6) in group 2. The authors conclude that long-term treatment of hyperthyroidism with MMI is safe and that complications and expense of the treatment do not exceed those of ^{131}I therapy.

42. (4) **Cooper DS.** Antithyroid drugs. N Engl J Med 2005;352:905–917.

Excellent review article on the mechanism of action, pharmacology, clinical indications, practical considerations, side effects of these drugs and their use in patients with various underlying causes of hyperthyroidism.

Antithyroid Drugs Plus LT4

43. (2) **Hashizume K,** et al. Administration of thyroxine in treated Graves' disease: Effects on the level of antibodies to thyroid-stimulating hormone receptors and on the risk of recurrence of hyperthyroidism. N Engl J Med 1991;324:947–953.

This prospective, randomized, placebo-controlled study evaluated the effectiveness of LT4 in decreasing TSAb levels and rate of recurrence of Graves hyperthyroidism after normalizing thyroid hormone secretion with MMI in 109 patients with untreated Graves hyperthyroidism. All patients received MMI and were euthyroid by 6 months. Patients were randomly assigned to receive 100 μg of LT4 and 10 mg of methimazole, or to placebo and 10 mg of MMI. After 1 year, MMI was discontinued; LT4 or placebo was continued for 3 more years. TSAb levels decreased after 1 month of treatment with LT4 and MMI but did not change in patients receiving placebo and MMI ($p < 0.01$). After withdrawal of MMI, TSAb levels decreased further in patients receiving LT4 but increased in those receiving placebo ($p = 0.01$). Within 3 years of discontinuing MMI, hyperthyroidism recurred in 2% of patients receiving LT4 and in 35% of those receiving placebo ($p < 0.001$).

44. (1) **McIver B,** et al. Lack of effect of thyroxine in patients with Graves' hyperthyroidism who are treated with an antithyroid drug. N Engl J Med 1996;334:220–224.

This prospective, randomized controlled trial evaluated whether addition of LT4 to ATD therapy in Graves disease reduces relapse rates of hyperthyroidism in 111 patients with Graves hyperthyroidism. All patients received 40 mg of carbimazole (CBZ) daily for 1 month. Next, one group received CBZ for 17 months, and the other group received CBZ plus LT4 for 17 months, followed by LT4 alone for 18 months. In the CBZ group, this dosage was adjusted to maintain normal serum TSH levels. In the CBZ-LT4 group, the dose of CBZ was not changed, but 100 mg of LT4 was added and the dosage adjusted to maintain serum TSH levels below 0.04 mIU/ml. At the time of analysis, 53 patients had completed at least 3 months of follow-up (median, 12 months) after withdrawal of CBZ. Hyperthyroidism recurred in 8 patients in each group with no difference in relapse rates between the groups.

45. **Andrade VA,** et al. The effect of methimazole pretreatment on the efficacy of radioactive iodine therapy in Graves' hyperthyroidism: One year follow up of a prospective randomized study. J Clin Endocrinol Metab 2001;86:3488–3493.

This study evaluated the effect of MMI pretreatment on the efficacy of ^{131}I therapy in 61 untreated patients with Graves hyperthyroidism. Exclusion criteria included previous treatment with ^{131}I or thyroidectomy, signs of moderate or severe ophthalmopathy, severe heart disease, debilitating conditions, and large, compressive goiters. ^{131}I alone ($n = 32$) or ^{131}I plus pretreatment with methimazole (30 mg/d; $n = 29$). ^{131}I was administered 4 days after drug discontinuation. The calculated ^{131}I dose was 200 μCi/g thyroid tissue as estimated by US, corrected by 24-hour ^{131}I uptake. Serum TSH, T4, and FT4 levels were measured 4 days before ^{131}I therapy, on the day of treatment, and then monthly for 1 year. About 80% of patients from both groups were cured (euthyroid or hypothyroid) 3 months after ^{131}I treatment. After 1 year, the groups were similar in terms of persistent hyperthyroidism (16% vs. 14%), euthyroidism (28% vs. 31%), or hypothyroidism (56% vs. 55%). Relapsed patients presented larger thyroid volume ($p = 0.002$), higher 24-hour ^{131}I uptake ($p = 0.022$), and

higher T3 levels (p = 0.002). Multiple logistic regression analysis identified T3 values as an independent predictor of therapy failure.

Radioiodine

46. (4) **Ross DS.** Radioiodine therapy for hyperthyroidism. N Engl J Med 2011;364:542–550.

    This excellent article reviews pathophysiology of hyperthyroidism, clinical use of ^{131}I for treatment of hyperthyroidism, considerations for selection of patients for different treatment modalities, adverse effects of RAI therapy, and areas of uncertainty.

47. (1) **Peters H,** et al. Reduction in thyroid volume after radioiodine therapy of Graves' hyperthyroidism: Results of a prospective, randomized, multicentre study. Eur J Clin Invest 1996;26:59–63.

    Ninety-two patients with Graves disease treated with ^{131}I were evaluated by US to assess reduction in thyroid volume. Patients received either a standard ^{131}I activity (555 MBq), or an activity calculated to deliver 100 Gy. Within 1 year of treatment, a median 71% volume reduction was observed, most of which occurred during the first 6 months. The standard group achieved a higher median dose and a more pronounced volume reduction (60% vs. 46% at 6 months, and 74% vs. 66% at 12 months, respectively) than the calculated group. The RR in thyroid size was just as marked in patients with large thyroids as in those with smaller glands, and the goiter prevalence was reduced from 73% to 16%, at 1 year after ^{131}I treatment.

48. (1) **Bartalena L,** et al. Relation between therapy for hyperthyroidism and the course of Graves' ophthalmopathy. N Engl J Med 1998;338:73–78.

    This randomized, controlled trial evaluated the effects of MMI, ^{131}I, and ^{131}I plus prednisone in 443 patients with Graves disease and mild (or no) ophthalmopathy. All patients received methimazole for 3 to 4 months and were then allocated to ^{131}I, ^{131}I and prednisone, or MMI. Progression or new ophthalmopathy occurred in 15% of patients treated with ^{131}I, and 3% of those receiving methimazole ($p < 0.001$); no patients on ^{131}I and prednisone developed or had progression of ophthalmopathy ($p < 0.001$ vs. ^{131}I). When ophthalmopathy was initially present, 67% of patients receiving ^{131}I plus prednisone improved compared with 4% who received methimazole ($p < 0.001$), and none receiving ^{131}I alone. In 65% of patients receiving only ^{131}I, transient or worsening ophthalmopathy occurred and 5% of patients developed persistent diplopia.

Thyroidectomy

49. (2) **Palit TK,** et al. The efficacy of thyroidectomy for Graves' disease: A meta-analysis. J Surg Res 2000;90:161–165.

    Meta-analysis of 35 studies including 7,241 patients who underwent either total thyroidectomy (TT) (n = 538) or subtotal thyroidectomy (ST) (n = 6703) for Graves disease. Hyperthyroidism persisted or recurred in 7% of patients. All patients who had TT became hypothyroid. Of the patients who underwent ST, 60% became euthyroid, 25% became hypothyroid, and 8% remained hyperthyroid. Permanent recurrent laryngeal nerve injury occurred in 1% of TT patients and 0.7% of ST patients and permanent hypoparathyroidism in 1.6% and 1%, respectively. A 9% decrease in hypothyroidism and 7% increase in euthyroidism was seen for each gram of thyroid remnant ($p < 0.0001$). Thyroidectomy successfully treated hyperthyroidism in 92% of patients.

β-Blockers

50. (1) **Jansson S,** et al. Oxygen consumption in patients with hyperthyroidism before and after treatment with beta-blockade versus thyrostatic treatment: A prospective randomized study. Ann Surg 2001;233:60–64.

    This prospective, randomized controlled trial was undertaken to evaluate the effect of thyrostatic treatment (tiamazol) compared with selective (metoprolol) and nonselective (propanolol) β-blockade on whole-body metabolism in 28 hyperthyroid women undergoing surgery as treatment of their hyperthyroidism. Six euthyroid women, with benign thyroid adenomas, served as controls. Whole-body O_2 consumption and CO_2 production were measured. Tiamazol normalized O_2 consumption and induced signs of anabolism. Propanolol (not metoprolol) reduced elevated O_2 consumption by 54%. Body weight was stable after specific and nonspecific β-blockade, which led to relief of symptoms in 90% of patients.

Hypothyroidism

Levothyroxine

51. (2) **Fish LH,** et al. Replacement dose, metabolism and bioavailability of levothyroxine in the treatment of hypothyroidism: Role of triiodothyronine in pituitary feedback in humans. N Engl J Med 1987;316:764–770.

    This prospective controlled cohort study was undertaken to determine adequate replacement dose of LT4 in 19 patients with hypothyroidism of different etiology; 66 healthy volunteers served

as controls. Results showed that the mean replacement dose was 112 ± 19 μg/d. TSH levels of patients on LT4 replacement returned to normal when T3 concentrations were similar to those of controls but when serum T4 levels were higher than those of controls (11.3 vs. 8.7 mg/dl; $p < 0.001$)

Subclinical Hypothyroidism

52. (2) **Danese MD,** et al. Effect of thyroxine therapy on serum lipoproteins in patients with mild thyroid failure: A quantitative review of the literature. J Clin Endocrinol Metab 2000;85:2993–3001.

Systematic review of the literature (1966–1999) assessing changes in serum lipid levels after treatment with LT4; 13 studies with 247 patients were included. The mean reduction in total cholesterol was 20.20 mmol/l (95% CI, 0.20 mmol/l; 20.09–20.34), and it was directly proportional to its baseline concentration. Studies enrolling hypothyroid under treated subjects showed larger reductions in total cholesterol after TSH normalization than studies of untreated patients with SCH (20.44 vs. 20.14 mmol/l; $p = 0.05$). LDL cholesterol levels decreased to 20.26 mmol/l (95% CI, 20.12–20.41). High-density lipoprotein (HDL) and triglyceride levels did not change.

53. (2) **Meier C,** et al. TSH-controlled L-thyroxine therapy reduces cholesterol levels and clinical symptoms in subclinical hypothyroidism: A double-blind, placebo-controlled trial. J Clin Endocrinol Metab 2001;86:4860–4866.

This randomized, double-blind, placebo-controlled study evaluated the effect of physiologic, TSH-guided LT4 treatment on serum lipids and clinical symptoms in 66 women with SCH. Treatment included LT4 with dosage guided by blinded TSH monitoring, resulting in euthyroid TSH levels (3.1 ± 0.3 mIU/l) for 48 weeks. Results indicated that in the LT4 group, total and LDL cholesterol were reduced by 4% ($p = 0.015$) and 8% ($p = 0.004$), respectively. LDL cholesterol reduction was larger in patients with TSH levels over 12 mIU/l or high LDL cholesterol at baseline. HDL cholesterol, triglycerides, apo-AI, and Lp(a) levels remained unchanged. Clinical scores of symptoms and signs of hypothyroidism improved ($p = 0.02$).

54. **Correia N,** et al. Evidence for a specific defect in hippocampal memory in overt and subclinical hypothyroidism. J Clin Endocrinol Metabol 2009;94:3789–3797.

This prospective, open-labeled interventional study was conducted to assess declarative memory in overt and SCH patients before and after LT4 replacement and in matched normal subjects. Twenty-one hypothyroid and seventeen SCH patients underwent neuropsychological tests at baseline and 3 and 6 months after LT4 replacement. Normal subjects were studied at the same time points.

Tests of spatial, verbal, associative, and working memory; attention; and response inhibition and the Hospital Anxiety and Depression Scale were administered. Baseline deficits in spatial, associative, and verbal memory, which rely upon the integrity of the hippocampal and frontal areas, were identified in patients with overt hypothyroidism. Spatial memory and verbal memory were also impaired in SCH patients. TSH levels correlated negatively with these deficits. After LT4 replacement, verbal memory normalized. Spatial memory normalized in the SCH group but remained impaired in the hypothyroid group in which associative memory deficits persisted as well. Hospital Anxiety and Depression Scale scores did not correlate with cognitive function. Cognitive impairment occurs in SCH and more markedly in overt hypothyroidism. These impairments appear predominantly mnemonic in nature, suggesting that the etiology is not indicative of general cognitive slowing. The authors propose that these deficits may reflect an underlying disruption of normal hippocampal function and/or connectivity.

55. (1) **Cooper DS,** et al. L-Thyroxine therapy in sub-clinical hypothyroidism: A double-blind, placebo-controlled trial. Ann Intern Med 1984;101:18–24.

Thirty-three patients with SCH were randomly assigned to receive placebo or LT4 therapy (double-blind) and observed during follow-up for 1 year with thyroid function tests, serum lipids, basal metabolic rate, and a questionnaire on hypothyroid symptoms. The placebo group showed no changes in thyroid function or indices of thyroid hormone action. In the LT4-treated group, serum lipids did not change. Symptoms improved in 57% of patients on LT4 and in 25% patients receiving placebo ($p < 0.05$).

56. **Parle J,** et al. A randomized controlled trial of the effect of thyroxine replacement on cognitive function in community-living elderly subjects with subclinical hypothyroidism: the Birmingham Elderly Thyroid study. J Clin Endocrinol Metabol 2010;95:3623–3632.

This double-blind, placebo-controlled RCT was undertaken in the United Kingdom to determine whether T4 replacement therapy in SCH improves cognitive function.

Ninety-four subjects aged 65 years and over (57 females, 37 males) with SCH were recruited from a population of 147 identified by screening. T4 or placebo was given at an initial dosage of one tablet of either placebo or 25 μg T4 per day for 12 months. Thyroid function tests were performed at eight weekly intervals with dosage adjusted in one-tablet increments to achieve TSH within the reference range for subjects in treatment arm. Fifty-two subjects received T4

while forty-two received placebo. Mini-Mental State Examination, Middlesex Elderly Assessment of Mental State (covering orientation, learning, memory, numeracy, perception, attention, and language skills), and Trail-Making A and B were administered. Eighty-two percent and eighty-four percent in the T4 group achieved euthyroidism at 6- and 12-month intervals, respectively. Cognitive function scores demonstrated no significant changes over time and no between-group difference at 6 and 12 months. This RCT provides no evidence for treating elderly subjects with SCH with T4 replacement therapy to improve cognitive function.

LT4 plus T3

57. (1) **Bunevicius R,** et al. Effects of thyroxine as compared with thyroxine plus triiodothyronine in patients with hypothyroidism. N Engl J Med 1999;340:424–429.

    Randomized, double-blind, crossover study designed to compare the effects of LT4 alone with those of LT4 plus T3 on thyroid hormone actions in the brain, pituitary gland, and other organs in patients with hypothyroidism. Thirty-three patients on replacement doses of LT4 for chronic autoimmune thyroiditis ($n = 16$) or on suppressive doses of LT4 after near-TT for thyroid cancer ($n = 17$) were randomized to receive LT4 alone for 5 weeks, then LT4 + T3 for 5 weeks, or vice versa and then to the alternative treatment. LT4 was given as 50 μg tablets at each patient's usual total dose, but 50 μg of the dose was replaced by a capsule containing either 50 μg of LT4 or 12.5 mg of T3. On the last day of each treatment period, all patients had measurements of TSH, thyroid hormones, cholesterol, triglycerides, and SHBG, and assessments of cognitive function and psychological state. Among 17 scores on tests of cognitive performance and assessments of mood, 6 were better or closer to normal after treatment with LT4 + T3. Similarly, among 15 visual-analogue scales used to indicate mood and physical status, results for 10 were better after treatment with LT4 + T3.

58. (1) **Sawka AM,** et al. Does a combination regimen of thyroxine (T4) and 3,5,3′-triiodothyronine improve depressive symptoms better than T4 alone in patients with hypothyroidism? Results of a double-blind, randomized, controlled trial. J Clin Endocrinol Metab 2003;88:4551–4555.

    This prospective, randomized, double-blind, placebo-controlled study evaluated whether combination of LT4 + T3 improves depressive symptoms better than LT4 alone in patients with hypothyroidism. Forty hypothyroid individuals with depressive symptoms taking a stable dose of LT4 were randomized to receive LT4 plus placebo or combination of LT4 + T3 for 15 weeks. Patients receiving combination therapy had their dose of LT4 reduced by 50%, and 12.5 μg of T3 was started twice daily and doses were adjusted to keep normal TSH levels. Compared with the group taking LT4 alone, the group taking both LT4 + T3 did not report any improvement in self-rated mood and well-being scores that included all subscales of the Symptom Checklist-90, the Comprehensive Epidemiological Screen for Depression, and the Multiple Outcome Study ($p > 0.05$ for all indexes).

59. (1) **Clyde PW,** et al. Combined levothyroxine plus liothyronine compared with levothyroxine alone in primary hypothyroidism: a randomized controlled trial. JAMA 2003;290:2952–2958.

    Randomized, parallel-group study design. Forty-six hypothyroid patients (most with autoimmune thyroiditis) were randomized to continue their current dose of LT4 ($n = 23$) or to receive 50 μg less than their usual LT4 dose, with the difference being replaced by T3 at a dose of 6.5 μg twice daily for 4 months ($n = 23$). LT4 doses were adjusted in both groups to maintain normal TSH levels. The HRQL questionnaire scores improved significantly in both the control group (23%; $p < 0.001$) and the combination therapy group (12%; $p = 0.02$), but these changes were statistically similar ($p = 0.54$). In 12 of 13 neuropsychological tests, outcomes between groups were not significantly different; the remaining test (Grooved Pegboard) showed better performance in the control group.

60. (1) **Walsh JP,** et al. Combined thyroxine/liothyronine treatment does not improve well-being, quality of life, or cognitive function compared to thyroxine alone: a randomized controlled trial in patients with primary hypothyroidism. J Clin Endocrinol Metab 2003;88:4543–4550.

    Double-blind, controlled trial with a crossover design in which 110 hypothyroid patients were randomized to receive their usual LT4 dose or substituting 10 μg of T3 for 50 μg of the patients' usual T(4) dose. No significant ($p > 0.05$) difference between LT4 and combined LT4/T3 treatment was demonstrated on cognitive function, QOL scores, Thyroid Symptom Questionnaire scores, subjective satisfaction with treatment, or eight of ten visual analogue scales assessing symptoms. For the General Health Questionnaire-28 and visual analogue scales assessing anxiety and nausea, scores were significantly ($p < 0.05$) worse for combined treatment than for LT4 alone. Serum TSH was lower during LT4 treatment than during combined LT4/T3 treatment, a potentially confounding factor; however, subgroup analysis of subjects with comparable serum TSH concentrations during each treatment showed no benefit from combined treatment compared with LT4 alone.

61. **Fadeyev VV,** et al. Combined therapy with L-thyroxine and L-triiodothyronine compared to L-thyroxine alone in the treatment of primary hypothyroidism. Hormones 2010;9:245–252.

This randomized, controlled trial was conducted in 36 hypothyroid premenopausal women to compare various parameters in patients with hypothyroidism receiving either monotherapy with L-thyroxine (LT4) or combination therapy with LT4 and L-triiodothyronine (LT3). Group A ($n = 20$) received only LT4, while group B received the combination LT4 and LT3. The treatment period lasted for 6 months. At baseline, the various parameters examined did not differ in the two groups. No significant difference between monotherapy and combined therapy was demonstrated on TSH level, ECG monitoring, densitometry, or thyroid symptoms score. The lipid profile was better during combined treatment compared to LT4 alone; in group A during treatment with LT4, the levels of cholesterol and LDL cholesterol were unchanged, while in group B, total cholesterol and LDL decreased ($p < 0.05$). The changes in osteocalcin levels did not differ in the two groups, whereas markers of bone resorption at the end of therapy were higher in the group with combination therapy, compared to monotherapy.

62. (1B) **Escobar-Morreale HF,** et al. Thyroid hormone replacement therapy in primary hypothyroidism: a randomized trial comparing L-thyroxine plus liothyronine with L-thyroxine alone. Ann Intern Med 2005;142:412–424.

Twenty-eight women with overt primary hypothyroidism were randomized to receive LT4 100 μg/d (standard treatment), or combination LT4 75 + T3 5 μg/d, for 8-week periods in a double-blind, crossover design. All patients also received LT4, 87.5 + T3, 7.5 μg/d (add-on combination treatment), for a final 8-week period. Primary outcomes included serum thyroid hormone levels, results of QOL and psychometric tests, and patients' preference. Combination treatment led to lower FT4 levels, slightly higher TSH levels, and unchanged FT3 levels. No improvement was observed in the other primary end points after combination treatment, with the exception of the Digit Span Test, in which the mean backward score and the mean total score increased slightly. The add-on combination treatment resulted in overreplacement. Levels of TSH decreased by 0.85 mU/l and serum FT3 levels increased by 0.8 pmol/l compared with standard treatment; 10 patients had levels of TSH that were below the normal range. Twelve patients preferred combination treatment, six patients preferred the add-on combination treatment, two patients preferred standard treatment, and six patients had no preference ($p = 0.015$).

Thyroid Nodules

Epidemiology

63. **Vander JB,** et al. The significance of nontoxic thyroid nodules: Final report of a 15 year study of the incidence of thyroid malignancy. Ann Intern Med 1968;69:537–540.

A sample of 4,469 people from the city of Framingham, Massachusetts, randomly selected from the total population of 10,000 (in 1948) and 740 volunteers were studied with physical examination and several laboratory tests every 2 years and observed for up to 15 years. Of the 5,127 participants, 4% had nontoxic thyroid nodules, none of which showed evidence of malignancy after 15 years of follow-up. The 15-year incidence rate of new thyroid nodules was 1.4%.

64. **Ezzat S,** et al. Thyroid incidentalomas: Prevalence by palpation and ultrasonography. Arch Intern Med 1994;154:1838–1840.

This prospective cohort study assessed the prevalence of thyroid nodules in the community and compared findings by palpation and HRUS in 100 asymptomatic North American subjects without known thyroid disease. Of these participants, 21% had palpable nodules (9% solitary nodules, 12% multiple nodules). By US measurement, 22% of patients had solitary nodules and 45% had multiple nodules. The prevalence of nodules was greater in women (72% vs. 41%; $p < 0.02$). The concordance rate between US and palpation was 49%.

65. (2) **Guth S,** et al. Very high prevalence of thyroid nodules detected by high frequency (13 MHz) ultrasound examination. Eur J Clin Invest 2009;39:699–706.

In this cohort, 635 consecutive patients (67% male, mean 56.7 years) presenting for a preventive health checkup underwent high-resolution US screening of the thyroid gland using a 13-MHz linear scanner and measurement of the basal TSH value. Size and degree of vascularization of the thyroid gland and of nodules were determined and analyzed retrospectively. In 432 of these patients (68%), thyroid nodules could be detected with an increasing incidence with age, in 338 without goiter. Mean thyroid size was 12.3 ml for women and 20.5 ml for men correlating strongly with body weight. Fifty-three percent of the nodules were smaller than 5 mm. Incidence of thyroid dysfunction was only 4%. No cancerous lesions could be found. This is a significantly higher prevalence than previously reported in the Papillon study (33%) and attributed to increased detection with the higher resolution of the US scanner.

66. **Mortensen JD,** et al. Gross and microscopic findings in clinically normal thyroid glands. J Clin Endocrinol Metab 1955;15:1270–1280.

Thyroid glands from 1,000 subjects without previous evidence of thyroid disease were removed during routine autopsy and examined for macroscopic lesions. Sixty-six subjects were excluded because of clinical evidence that their thyroid may not have been normal and 113 others because of inadequate recording of clinical examination of the thyroid. In the remaining 821 glands, 12% contained a single nodule and 38% had multiple nodules. The size of these nodules varied from 2 mm to 7.5 cm in diameter, and 36% of nodular glands contained one or more nodules larger than 2 cm. Benign and malignant nodules occurred with about the same frequency, but malignant nodules were more common in women, after the age of 40 years, and in patients living in so-called goiter belts. Primary occult carcinoma was found in 17 patients (4% of the nodular thyroid glands).

67. **Tan GH, Gharib H, Reading CC.** Solitary thyroid nodule: Comparison between palpation and ultrasonography. Arch Int Med 1995;155:2418–2423.

    This retrospective review aimed to determine the accuracy of clinical palpation in the diagnosis of solitary thyroid nodule in comparison with ultrasonographic findings.

    The authors compared concordance rate between palpation and US in 193 patients who were diagnosed clinically with NTD and who underwent US of the thyroid. Nodules were categorized as "solitary" or "dominant nodule of a multinodular gland." Concordance rates were measured between results of palpation and US findings. Of 151 patients included in the study, 78 had solitary nodules on US and 73 had multiple nodules. Of those with multiple nodules, 49 had 2 nodules and 24 had 3 or more nodules. Of clinically palpable nodules, 89% were 1 cm or greater in diameter. In 72% of the patients with multiple nodules, the other nodules not identified on palpation were less than 1 cm in diameter. The overall concordance rate between the size of the solitary or the dominant nodule estimated by palpation and the US size was 72%. These results suggest that (1) a palpable solitary nodule represents a multinodular gland in about 50% of patients, (2) clinical palpation is less sensitive than US in identifying multiple nodules, and (3) palpation is reliable only if a nodule is at least 1 cm in diameter

68. (3) **Frates MC,** et al. Prevalence and distribution of carcinoma in patients with solitary and multiple thyroid nodules on sonography. J Clin Endocrinol Metabol 2006;91:3411–3417.

    This retrospective observational cohort study conducted in a tertiary care center was carried out from 1995 to 2003 to determine prevalence, distribution, and sonographic features of thyroid cancer in patients with solitary and multiple thyroid nodules. Patients with one or more thyroid nodules larger than 10 mm who had US-FNA were included in the study. The main outcome measures were prevalence and distribution of thyroid cancer and the predictive value of demographic and sonographic features. A total of 1,985 patients underwent FNA of 3,483 nodules. The prevalence of thyroid cancer was similar between patients with a solitary nodule (14.8%) and patients with multiple nodules (14.9%) ($p = 0.95$). A solitary nodule had a higher likelihood of malignancy than a nonsolitary nodule ($p < 0.01$). In patients with multiple nodules larger than 10 mm, cancer was multifocal in 46%, and 72% of cancers occurred in the largest nodule. The combination of patient gender ($p < 0.02$), whether a nodule is solitary versus one of multiple ($p < 0.002$), nodule composition ($p < 0.01$), and presence of calcifications ($p < 0.001$) can be used to assign risk of cancer to each individual nodule. The authors conclude that in a patient with one or more thyroid nodules larger than 10 mm, the likelihood of thyroid cancer per patient is independent of the number of nodules, whereas the likelihood per nodule decreases as the number of nodules increases. Sonographic characteristics can be used to prioritize nodules for FNA based on their individual risk of cancer.

69. (3) **Gharib H, Goellner JR.** Fine needle aspiration of the thyroid: An appraisal. Ann Intern Med 1993;118:282–289.

    This article is a comprehensive review of the literature and the authors' experience with more than 11,000 biopsies on the usefulness, advantages, limitations, and diagnostic accuracy of FNA biopsy in the diagnosis and management of thyroid nodules and thyroid cancer.

Treatment

70. (1) **Gharib,** et al. American Association of Clinical Endocrinologists and Associazione Medici Endocrinologi medical guidelines for clinical practice for the diagnosis and management of thyroid nodules. Endocr Practice 2006;12:63–102.

    These guidelines covering diagnostic and therapeutic aspects of thyroid nodular disease were prepared as a collaborative effort between the American Association of Clinical Endocrinologists (AACE), the Associazione Medici Endocrinologi (Italian Association of Clinical Endocrinologists) (AME), and the European Thyroid Association (ETA). The AACE protocol for standardized production of clinical practice guidelines was followed to rate the evidence level of each reference (on a scale of 1–4) and to link the guidelines to the strength of recommendations on the basis of grade designations A (action based on strong evidence) through D (action not based on any evidence or not recommended).

71. (1) **Cooper DS,** et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19:1167–214.

Relevant articles through December 2008 were reviewed by the ATA task force and categorized by topic and level of evidence according to a modified schema used by the United States Preventative Services Task Force. The authors created evidence-based recommendations to assist in the clinical management of patients with thyroid nodules and differentiated thyroid cancer. The guidelines represent contemporary optimal care for patients with these disorders.

72. (4) **Hermus AR,** Huysmans DA. Treatment of benign nodular thyroid disease. N Engl J Med 1998;338:1438–1447.

Excellent review of available treatment modalities for toxic and nontoxic uninodular and multi-NTD, including advantages and disadvantages of each modality.

LT4 Suppressive Therapy

73. (2) **Csako G,** et al. Assessing the effects of thyroid suppression on benign solitary thyroid nodules: A model for using quantitative research synthesis. Medicine 2000;79:9–26.

Systematic review of 30 published reports on the efficacy of LT4 suppressive therapy in solitary thyroid nodules. The study's authors also report results of a survey on the opinion of all endocrinologists working at the National Institutes of Health and perform a meta-analysis of five randomized controlled trials that met the following criteria: documentation of TSH suppression, US measurement of thyroid nodules, and assessment of clinically significant (0.50%) reduction in nodule size. The percentage of patients with nodule size reduction exceeding 50% was higher in the treatment groups than in the cotrols (19% vs. 10%). LT4 suppressive therapy was associated with a 2.11 (CI, 0.90–4.94; $p = 0.086$) to 2.49 (CI, 1.41–4.40; $p = 0.008$) times greater probability of achieving at least a 50% reduction in nodule size using a random and fixed effects models, respectively; effect sizes were heterogeneous.

74. **Wemeau JL,** et al. Effects of thyroid-stimulating hormone suppression with levothyroxine in reducing the volume of solitary thyroid nodules and improving extranodular nonpalpable changes: A randomized, double-blind, placebo-controlled trial by the French Thyroid Research Group. J Clin Endocrinol Metabol 2002;87:4928–4934.

In this prospective multicenter, double-blind, placebo-controlled RCT, 123 patients with a single palpable benign nodule were included and randomly allocated to an 18-month treatment with LT4 or placebo. Individual dose was adjusted to allow a serum TSH level below 0.3 mIU/l. Clinical and US nodule characteristics were assessed before treatment and 3, 6, 12, and 18 months thereafter. The largest mean nodule size assessed on palpation and largest volume, assessed by US, decreased in the LT4 group and increased slightly in the placebo group (size, -3.5 ± 7 mm vs. $+0.5 \pm 6$ mm [$p = 0.006$]; volume, -0.36 ± 1.71 ml vs. $+0.62 \pm 3.67$ ml [$p = 0.01$], respectively). The proportion of clinically relevant volume reduction (≥50%) rose significantly in the LT4 group (26.6% vs. 16.9% [$p = 0.04$]). The proportion of patients with a reduced number of infraclinical additional nodules was higher in the LT4 group (9.4% vs. 0 [$p = 0.04$]). This study concludes that suppressive LT4 therapy is effective in reducing solitary thyroid nodule volume and improving infraclinical extranodular changes.

75. (1) **Castro MR,** et al. Effectiveness of levothyroxine suppressive therapy in benign solitary thyroid nodules: A meta-analysis. J Clin Endocrinol Metab 2002;87:4154–4159.

This is a systematic review of the literature and meta-analysis of a randomized controlled trial, fulfilling the following inclusion criteria: solitary thyroid nodules, benign by FNA, treatment and follow-up of at least 6 months, documented suppression of TSH, measurement of thyroid nodule volume by US, and response to therapy defined as an at least 50% reduction in volume from findings at baseline. Six randomized controlled trials (1987–1999) with 346 patients were included in this meta-analysis. The overall effect size showed a relative risk of 1.9 (95% CI, 0.95–3.81) favoring a treatment effect. Results were highly sensitive to changes in statistical analysis, especially if the method used ignored heterogeneity among the effect sizes.

76. **Berghout A,** et al. Comparison of placebo with L-thyroxine alone or with carbimazole for treatment of sporadic non-toxic goitre. Lancet 1990;336:193–197.

The efficacy of suppressive doses of LT4 (2.5 mg/kg/d) alone or combined with CBZ (40 mg daily) was studied in 78 patients with sporadic nontoxic goiter in a prospective, placebo-controlled, double-blind, randomized controlled trial. Treatment was given for 9 months, with 9 months of follow-up. A response to treatment as measured by US was found in 58% of the LT4 group, 35% of the LT4/CBZ group, and 5% of the placebo group. The mean reduction of thyroid volume in those who responded was 25%. After discontinuing treatment, thyroid volume increased in the responders and had returned to baseline values after 9 months of follow-up. In the placebo group, mean thyroid volume had increased by 20% at 9 months and 27% at 18 months.

77. (1) **Uzzan B,** et al. Effects of bone mass of long-term treatment with thyroid hormones: A meta-analysis. J Clin Endocrinol Metab 1996;81:4278–4289.

This meta-analysis evaluated the effect of long-term LT4 therapy on bone mineral density (BMD). It includes 41 controlled, cross-sectional studies, which included about 1,250 patients. Studies with women receiving estrogen therapy were a priori excluded. Suppressive LT4 therapy was associated with significant bone loss in postmenopausal but not in premenopausal women. Conversely, replacement therapy was associated with bone loss in premenopausal but not in postmenopausal women. The adverse effect of LT4 was more marked on cortical than on trabecular bone.

78. (2) **Sawin CT,** et al. Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older persons. N Engl J Med 1994;331:1249–1252.

This was a 10-year cohort study of participants in the original Framingham Heart Study. Its purpose was to determine whether a low serum TSH level in adults 60 years of age or older is a risk factor for development of atrial fibrillation. The population consisted of 2,007 adults aged 60 years or older at baseline assessment. About 3% of participants had low (0.1 mU/l or lower) TSH levels, 9% had slightly low (0.1–0.4 mU/l) levels, 79% had normal (0.4–5.0 mU/l) levels, and 9% had high (5.0 mU/l) levels. During follow-up, atrial fibrillation developed in 192 participants. The cumulative incidence of atrial fibrillation in 10 years was 28% in the low-level group, 16% in the slightly low-level group, 11% in the normal-level group, and 15% in the high-level group. When adjusted for age, gender, and all risk factors, the relative risk for new atrial fibrillation in the low-level group compared with that in the normal-level group was 3.1 (95% CI, 1.7–5.5; $p = 0.001$); for the slightly low-level group, relative risk was 1.6 (CI, 1.0–2.5; $p = 0.05$). Results were similar when subjects taking thyroid hormones were excluded.

Radioiodine

79. (2) **Nygaard B,** et al. Radioiodine treatment of multinodular non-toxic goitre. BMJ 1993;307:828–832.

This observational study investigated the long-term effect of ^{131}I on thyroid size and function in 69 patients with nontoxic multinodular goiter causing compressive symptoms or cosmetic concerns, who had contraindication to or had refused surgery. Fifty-six patients received a single dose of ^{131}I, twelve received two doses, and one received four doses. In 9 of 45 patients who received one dose and remained euthyroid, median thyroid volume was reduced by 60% ($p = 0.0001$) by 24 months; half of this amelioration occurred during the first 3 months. Patients treated with two doses, and those in whom hypothyroidism developed, also had a significant reduction in thyroid volume. Cumulative 5-year risk of development of hypothyroidism was 22% (CI, 5%–38%).

80. (2) **Huysmans DAKC,** et al. Long-term results of two schedules of radioiodine treatment for toxic multinodular goiter. Eur J Nucl Med 1993;20:1056–1062.

This prospective study evaluated the long-term effectiveness of low-dose ^{131}I (150 MBq; group A) and of calculated dose adjusted for thyroid weight (1.85–3.7 MBq/g; group B) in 103 patients with toxic multinodular goiter. Mean follow-up was 4 to 5 years. Hyperthyroidism was successfully reversed in 73% of group A and 88% of group B, with development of hypothyroidism in 7% in each group. Patients treated with calculated doses required significantly fewer treatments (1.3 ± 0.1 vs. 2.2 ± 0.2), and the percentage of patients adequately treated with a single dose was more than twice as high in group B (66% vs. 27%). Euthyroidism was achieved sooner with calculated doses (0.6 years in group B vs. 1.5 years in group A).

81. (1) **Wesche,** et al. A randomized trial comparing levothyroxine with radioactive iodine in the treatment of sporadic nontoxic goiter. J Clin Endocrinol Metabol 2001;86:998–1005.

This RCT was performed in patients with sporadic nontoxic nodular goiter to compare efficacy and side effects of ^{131}I therapy with suppressive LT4 treatment. Sixty-four patients were randomized after stratification for sex and menopausal age to receive ^{131}I (4.44 MBq/g thyroid; group A) or suppressive LT4 treatment aiming at TSH values between 0.01 and 0.1 mU/l (group B). The main outcome measurements after 2 years were goiter size by ultrasound, serum thyroid function tests, markers of bone turnover, and BMD. Fifty-seven patients completed the trial. Goiter size was reduced after 2 years by 44% in group A and by 1% in group B ($p < 0.001$). Nonresponders (goiter reduction <13%) were 1 of 29 patients in group A and 16 of 28 patients in group B. In responders, goiter reduction in group A (46%) was greater than in group B (22%; $P < 0.005$). In group A, 45% of patients developed hypothyroidism. In group B, 10 patients experienced thyrotoxic symptoms, requiring discontinuation of treatment in 2. Markers of bone formation and bone resorption increased in group B, related to a mean decrease of 3.6% of BMD at the lumbar spine after 2 years ($P < 0.001$), both in pre- and postmenopausal women. No changes in BMD were observed in group A.

82. (2) **Nieuwlaat WA,** et al. Pretreatment with a single, low dose of recombinant human thyrotropin allows dose reduction of radioiodine therapy in patients with nodular goiter. J Clin Endocrinol Metab 2003;88:3121–3129.

The authors had previously demonstrated that pretreatment with a single, low dose of rhTSH doubles 24-hour RAIU in patients with nodular goiter. In this prospective study, the authors

report on the safety and efficacy of therapy with a reduced dose of ^{131}I after pretreatment with rhTSH. Twenty-two patients with nodular goiter received ^{131}I therapy, 24 hour after IM administration of 0.01 (n = 12) or 0.03 (n = 10) mg rhTSH. Pretreatment with rhTSH allowed dose reduction of ^{131}I therapy by a factor of 1.9 ± 0.5 in the 0.01-mg and by a factor of 2.4 ± 0.4 in the 0.03-mg rhTSH group ($p < 0.05$, 0.01 vs. 0.03 mg rhTSH). One year after treatment, thyroid volume (TV) reduction was 35 ± 14% (0.01 mg rhTSH) and 41 ± 12% (0.03 mg rhTSH). In both groups, smallest cross-sectional area of the tracheal lumen increased significantly. Individual peak FT4 levels, reached between 1 and 28 days after ^{131}I treatment, were above the normal range in 12 patients. TRAbs became positive in four patients after therapy. Hyperthyroidism developed in three of these four patients between 23 and 25 weeks after therapy. In patients with nodular goiter pretreatment with a single, low dose of rhTSH allowed approximately 50% to 60% reduction of the therapeutic dose of RAI without compromising the efficacy of TV reduction.

83. (2) **Fast S,** et al. Recombinant human thyrotropin-stimulated radioiodine therapy of nodular goiter allows major reduction of the radiation burden with retained efficacy. J Clin Endocrinol Metabol 2010;95:3719–3725.

In a double-blind, placebo-controlled setup, 90 patients with a nontoxic nodular goiter were randomized to either 0.1 mg rhTSH (n = 60) followed by a thyroid dose of 50 Gy or placebo followed by 100 Gy (n = 30). At 12 months, the mean relative goiter volume reduction in the placebo and the rhTSH group were identical (35 ± 3%; p = 0.81). The median administered ^{131}I-activity was 170 MBq (45–1,269) in the rhTSH group and 559 MBq (245–3,530) in the placebo group (70% reduction, $p < 0.0001$). In both groups, goiter-related symptoms were effectively relieved in the majority of patients. This is the first study to demonstrate that rhTSH not only increases the thyroid ^{131}I uptake but also potentiates the effect of ^{131}I-therapy, allowing a major reduction of the ^{131}I-activity without compromising efficacy. This approach is attractive in terms of minimizing posttherapeutic restrictions and in reducing the potential risk of radiation-induced malignancy.

84. (3) **Fast S,** et al. Dose-dependent acute effects of recombinant human TSH (rhTSH) on thyroid size and function: comparison of 0.1, 0.3 and 0.9 mg of rhTSH. Clin Endocrinology 2010;72:411–416.

This study was conducted to determine the effects of various doses of rhTSH on thyroid size and function. The effect of placebo, 0.1, 0.3, and 0.9 mg of rhTSH was examined in nine healthy male volunteers, in a paired design including four consecutive study rounds. Main outcome measures (TV estimation by US, and thyroid function—TSH, FT3, FT4—and Tg levels) were evaluated at baseline, 24, 48, 96 hours, 7 and 28 days after rhTSH. Following placebo or 0.1 mg rhTSH, the TV did not change significantly from baseline at any time. At 24 and 48 hours after administration of 0.3 mg rhTSH, the TV increased by 37.4% ± 12.3% (p = 0.03) and 45.3% ±16.1% (p = 0.05), respectively. After 0.9 mg rhTSH, the TV increased by 23.3% ±5.8% (p = 0.008) and 35.5% ± 18.4% (p = 0.02), respectively. The increase in serum FT3, FT4, and Tg was greater when administering 0.3 mg compared with 0.1 mg or 0.9 mg compared with 0.3 mg. After 0.1 mg rhTSH, the increase in FT3 and Tg was not significantly different from placebo, whereas the FT4 increase was significantly higher (p = 0.02). In healthy individuals, rhTSH-induced thyroid swelling and hyperthyroidism is rapid and dose dependent. These results suggest that these adverse effects are unlikely to be of clinical significance, following doses of rhTSH of 0.1 mg or less.

Percutaneous Ethanol Injection

85. (2) **Valcavi R and Frasoldati A.** Ultrasound-guided percutaneous ethanol injection therapy in thyroid cystic nodules. Endoc Practice. 2004. 10:269–275.

Controlled randomized study, involving 281 patients with benign thyroid cystic nodules. Inclusion criteria were local discomfort or cosmetic damage, cystic volume more than 2 ml, 50% or more fluid component, benignity confirmed by US-guided FNA biopsy, and euthyroidism. Exclusion criteria were inadequate, suspicious, or positive FNAB cytology, high serum calcitonin, and contralateral laryngeal cord palsy. By random assignment, 138 patients underwent simple cyst evacuation and 143 underwent cyst evacuation plus PEI. The amount of ethanol injected was 50% to 70% of the cystic fluid extracted. Before treatment, the mean nodule volume was similar in both groups (19.0 ± 19.0 ml PEI vs. 20.0 ± 13.4 ml in simple evacuation group). After 1 year, volumes were 5.5 ± 11.7 ml versus 16.4 ± 13.7 ml ($p < 0.001$), with a median 85.6% versus 7.3% reduction, respectively ($p < 0.001$), of the initial volume. Compressive and cosmetic symptoms disappeared in 74.8% and 80.0% of patients treated with PEI versus 24.4% and 37.4% of patients treated with simple evacuation, respectively ($p < 0.001$). Side effects were minor.

86. (1) **Bennedbaek FN, Hegedus L.** Treatment of recurrent thyroid cysts with ethanol: a randomized double-blind controlled trial. J Clin Endocrinol Metab 2003;88:5773–5777.

Sixty-six consecutive patients with recurrent and benign thyroid cysts (≥2 ml) were randomly assigned to either subtotal cyst aspiration, flushing with 99% ethanol, and subse-

quent complete fluid aspiration (n = 33), or to subtotal cyst aspiration, flushing with isotonic saline, and subsequent complete fluid aspiration (n = 33). In case of recurrence (defined as cyst volume >1 ml) at the monthly evaluations, the treatment was repeated but limited to a maximum of three treatments. Procedures were US-guided, and patients were followed for 6 months. Cure (defined as a cyst volume ≤1 ml at the end of follow-up) was obtained in 82% of patients treated with ethanol and in 48% of patients treated with saline (p = 0.006). In the ethanol group, 64% of patients were cured after one session only, compared with 18% in the saline group (p = 0.002). The chance of success decreased with the number of previous aspirations and with increasing cyst volume. Seven patients (21%) treated with ethanol had moderate to severe pain (median duration, 5 minutes), and one had transient dysphonia. Indirect laryngoscopy was performed before and after the last session and was normal in all patients. Flushing with ethanol may be a reasonable nonsurgical alternative for thyroid cysts that recur despite repeat aspirations.

Laser Thermal Ablation

87. (2) **Dossing H,** et al. Effect of ultrasound-guided interstitial laser photocoagulation on benign solitary solid cold thyroid nodules—a randomized study. Eur J Endocrinol 2005;152:341–345.

    Thirty euthyroid outpatients with a benign cold solitary solid thyroid nodule causing local discomfort were prospectively randomized to one session of LTA (n = 15) or observation (n = 15) and followed for 6 months. Thyroid nodule volume and total TV were assessed by US, and thyroid function was determined by routine assays before and during follow-up. Pressure and cosmetic complaints before and at 6 months were evaluated on a visual analogue scale. LTA was performed under US guidance. Nodule volume decreased significantly in the LTA group (median reduction was 44%) after 6 months (p = 0.001), and this reduction correlated with a substantial decrease in pressure symptoms and cosmetic complaints with no major side effects. In the control group, there was a nonsignificant increase in median nodule volume of 7% after 6 months.

88. (2) **Papini E,** et al. Ultrasound-guided laser thermal ablation for treatment of benign thyroid nodules. Endocr Pract 2004;10:276–283.

    Prospective observational cohort study, twenty patients fulfilling the following entry criteria were enrolled: (1) presence of a hypofunctioning thyroid nodule with a volume exceeding 8 ml, (2) benign cytologic findings, (3) local compression symptoms or patient concern, and (4) refusal of or ineligibility for surgical treatment. Under US monitoring, LTA was performed. Nodule volume was assessed by US at 1 and 6 months after LTA. Mean nodule volume reduction in comparison with baseline was 43.8% ± 8.1% at 1 month and 63.8% ± 8.9% at 6 months. LTA induced burning cervical pain, which rapidly decreased after the laser energy was turned off. Three patients (15%) required treatment with betamethasone for 48 hours. No patient had local bruising, cutaneous burning, or dysphonia.

Thyroid Cancer

Reviews

89. (4) **Mazzaferri EL, Kloos R.** Current approaches to primary therapy for papillary and follicular thyroid cancer. J Clin Endocrinol Metab 2001;86:1447–1463.

    This is an excellent review, covering risk stratification, staging systems, approaches to initial surgical management, ^{131}I remnant ablation, diagnostic WBS, ^{131}I therapy for residual disease, and thyroid hormone suppressive therapy in the management of papillary and follicular thyroid cancer.

Diagnosis

90. (4) **Belfiore A, La Rosa GL.** Fine-needle aspiration biopsy of the thyroid. Endocrinol Metab Clin North Am 2001;30:361–400.

    This article covers indications, technique, complications, cytologic diagnosis, diagnostic accuracy, and pitfalls of thyroid FNA biopsy and provides guidelines on how to use the information obtained by this procedure in the clinical management of thyroid nodules.

91. (4) **Torrens JI, Burch HB.** Serum thyroglobulin measurement: Utility in clinical practice. Endocrinol Metab Clin North Am 2001;30:429–467.

    This article provides information to allow a meaningful interpretation of Tg levels in the diagnosis and management of several thyroid disorders, with emphasis on differentiated thyroid cancer. Immunologic characteristics of Tg and TgAb and of several Tg assays and their potential pitfalls are discussed. Practical guidelines are provided for use of serum Tg in clinical practice

92. (2) **Frasoldati A,** et al. Role of thyroglobulin measurement in fine-needle aspiration biopsies of cervical lymph nodes in patients with differentiated thyroid cancer. Thyroid 1999;9:105–111.

In this prospective cohort, the authors measured Tg in the needle washout FNA biopsy of enlarged neck LNs in 23 patients awaiting surgery for DTC (n = 33 LN), 47 patients previously thyroidectomized for thyroid tumor (n = 89 LN), and 60 patients without thyroid disease (n = 94 LN). Immediately after aspiration biopsy, the needle was rinsed with 1 ml of normal saline solution and Tg levels were measured on the needle washout (FNAB-Tg). FNAB-Tg levels were markedly elevated in metastatic LN both in patients awaiting thyroidectomy (metastatic vs. negative LN, mean ± SEM, 16,593 ± 7,050 vs. 4.91 ± 1.61 ng/ml; $p < 0.001$) and in thyroidectomized patients (11,541 ±7,283 vs. 0.45 ± 0.07 ng/ml; $p < 0.001$). FNAB-Tg sensitivity, evaluated through histologic examination in 69 LN, was 84.0%. The combination of cytology plus FNAB-Tg increased FNAB sensitivity from 76% to 92.0%.

93. (3) **Hernandez,** et al. Usefulness of the determination of thyroglobulin in lymph node aspirates of patients with papillary thyroid carcinoma and positive antithyroglobulin antibodies. Endocrinologia y Nutricion 2009;56:447–451.

In order to study the utility of Tg determination in the washout of FNA (FNAB-Tg) of metastatic LNs in patients with PTC and positive serum TgAbs, the authors studied 11 patients (49.9 ± 11.8 years old, 70% females) with PTC and positive TgAb in which a WBS after ^{131}I treatment showed pathologic uptake in lymph cervical nodes. A US-FNAB was performed for cytologic research. Needle washout with 1 ml saline was employed to determine FNAB-Tg. In 16/17 suspicious nodes, Tg-FNAB concentration was elevated, and TgAb were negative in the washout obtained. WBS was able to detect 94% lymphadenopathies, whereas 76.5% were detected with US and 70.6% using cytology. The FNAB-Tg was positive in 94% of nodules, higher than the combination of US and FNAB cytology both together (88.2%). One hundred percent of pathologic nodules were detected using US plus FNAB-Tg.

94. (4) **Ledger GA,** et al. Genetic testing in the diagnosis and management of multiple endocrine neoplasia type II. Ann Intern Med 1995;122:118–124.

This review covers advances in the early diagnosis and treatment of MTC in patients with multiple endocrine neoplasia (MEN) 2 syndromes, clinical features, biochemical screening, and the usefulness and limitations of genetic testing, especially DNA and linkage analysis, as a means of early detection of individuals affected with the familial forms of MTC. It also reviews the correlation between results of genetic and biochemical testing and current screening recommendations in this disorder.

95. (1) **Kloos,** et al. Medullary thyroid cancer: management guidelines of the American Thyroid Association. Thyroid 2009;19:565–612.

This document by the ATA contains specific MTC clinical guidelines to bring together and update the diverse MTC literature and combine it with evidence-based medicine and the knowledge and experience of a panel of expert clinicians. Relevant articles were identified using a systematic PubMed search and supplemented with additional published materials. A total of 122 evidence-based recommendations were created and then categorized using criteria adapted from the United States Preventive Services Task Force, Agency for Healthcare Research and Quality. Clinical topics addressed in this scholarly dialog included: initial diagnosis and therapy of preclinical disease, initial diagnosis and therapy of clinically apparent disease, initial evaluation and treatment of postoperative patients, management of persistent or recurrent MTC, long-term follow-up and management, and directions for future research.

96. **Costante G,** et al. Predictive value of serum calcitonin levels for preoperative diagnosis of medullary thyroid carcinoma in a cohort of 5,817 consecutive patients with thyroid nodules. J Clin Endocrinol Metab 2007;92:450–455.

To evaluate the diagnostic accuracy of systematic calcitonin (CT) measurement in non-MEN-2 patients with NTD, 5,817 consecutive patients with NTD were studied. Serum CT levels were measured under basal conditions, and when basal values were greater than or equal to 20 and less than 100 pg/ml, testing was repeated after pentagastrin stimulation. Basal or stimulated levels greater than 100 pg/ml were indication for surgery. Fifteen cases of MTC and seven of C-cell hyperplasia (CCH) were identified. MTCs were diagnosed in all patients with basal CT more than 100 pg/ml. The four patients with basal CT greater than or equal to 50 and less than 100 pg/ml included two diagnosed with MTC and two with CCH. In 10 patients with basal levels greater than or equal to 20 and less than 50 pg/ml, histology confirmed the presence of MTC in four, four others had CCH, and the remaining two were negative for thyroid malignancy. Positive predictive values for basal CT levels in the preoperative diagnosis of MTC were 23.1% for values greater than or equal to 20 pg/ml, 100% for values greater than 100 pg/ml, 25% for levels greater than or equal to 50 and less than 100 pg/ml, and 8.3% for values greater than or equal to 20 and less than 50 pg/ml. Positive predictive values for the pentagastrin test (>100 pg/ml) were 40% in the entire series. CT screening of thyroid nodules is a highly sensitive test for early diagnosis of MTC, but confirmatory stimulation testing is necessary in most cases to identify true positive increases.

97. (4) **Cheung K,** et al. Calcitonin measurement in the evaluation of thyroid nodules in the United States: a cost-effectiveness and decision analysis. J Clin Endocrinol Metab 2008;93:2173–2180.

    To determine the cost-effectiveness (C/E) of routine calcitonin screening in adult patients with thyroid nodules in the United States, a decision model was developed for a hypothetical group of adult patients presenting for evaluation of thyroid nodules in the United States. Patients were screened using current ATA guidelines only, or ATA guidelines with routine serum calcitonin screening. Input data were obtained from the literature, the Surveillance Epidemiology and End Results and Healthcare Cost and Utilization Project's Nationwide Inpatient Sample databases, and the Medicare Reimbursement Schedule. Sensitivity analyses were performed for a number of input variables. C/E, measured in dollars per life years saved (LYS), was calculated. Addition of calcitonin screening to current ATA guidelines for the evaluation of thyroid nodules would cost $11,793 per LYS ($10,941–$12,646). When extrapolated to the national level, calcitonin screening for MTC in the United States would yield an additional 113,000 life years at a cost increase of 5.3%. Calcitonin screening C/E is sensitive to patient age and gender, and to changes in disease prevalence, specificity of FNA and calcitonin testing, calcitonin screening level, costs of testing, and length of follow-up. Routine serum calcitonin screening in patients undergoing evaluation for thyroid nodules appears to be cost-effective in the United States, with C/E comparable to the measurement of TSH, colonoscopy, and mammography screening.

Treatment

Surgery

98. (3) **Shaha AR,** et al. Prognostic factors and risk group analysis in follicular carcinoma of the thyroid. Surgery 1995;118:1131–1136.

    Review of 228 previously untreated patients with FTC during a 55-year period. Fifty-nine (26%) patients presented with Hürthle cell histology. There were 62 patients in the low-risk group, 84 in the intermediate-risk group, and 82 in the high-risk groups, with 10-year survival rates of 98%, 88%, and 56%, respectively, and 20-year survival rates of 97%, 87%, and 49%, respectively. Adverse prognostic factors included age over 45 years ($p < 0.001$), Hürthle cell variety ($p = 0.05$), extrathyroidal extension, tumor size that exceeds 4 cm, and presence of distant metastasis ($p < 0.001$). Gender, focus, and LN metastasis did not affect prognosis.

99. (2) **Samaan NA,** et al. The results of various modalities of treatment of well-differentiated thyroid carcinomas: A retrospective review of 1,599 patients. J Clin Endocrinol Metab 1992;75:714–720.

    This study of 1,599 patients with differentiated thyroid cancer analyzed impact of age, gender, histologic diagnosis, extent of disease at diagnosis, and surgical intervention on the cancer, and impact of surgical treatment, ^{131}I, and radiotherapy on outcomes. Patients were predominantly female (2.3:1), with papillary (81%) and intrathyroidal carcinomas (42%) at the time of diagnosis. Median follow-up was 11 years. Of these patients, 66% had TT, 7% received external radiation, and 46% had ^{131}I as part of treatment of the original disease; overall recurrence rate was 23% and the death rate 11%. Treatment with ^{131}I was the single most powerful prognostic indicator for increased disease-free intervals and overall survival ($p < 0.001$). Other predictors of better outcome included younger age, female gender, localized intrathyroidal papillary disease, and near-total or TT.

100. (2) **Mazzaferri EL, Jhiang SM.** Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. Am J Med 1994;97:418–428.

     Patients with PTC and FTC ($n = 1355$) treated at the U.S. Air Force hospital or Ohio State University hospital over the course of 40 years were evaluated to determine treatment outcomes. After 30 years, survival rate was 76%, recurrence rate 30%, and cancer death rate 8%. Recurrences were most frequent at the extremes of age (<20 and >59 years). Cancer mortality rates were lowest in patients younger than 40 years of age and thereafter increased with each decade of life. Thirty-year cancer mortality rates were highest in FTC patients. When patients with distant metastases at diagnosis were excluded, FTC and PTC mortality rates were similar (10% vs. 6%, respectively). The likelihood of cancer death was (1) increased by age over 40 years, tumor size 1.5 cm or larger, local tumor invasion, regional LN metastases, and delay in therapy of more than 12 months; (2) reduced by female gender, surgery more extensive than lobectomy, and ^{131}I plus thyroid hormone therapy; and (3) unaffected by tumor histologic type. Remnant ablation with ^{131}I reduced the recurrence rate to less than one-third the rate after thyroid hormone therapy alone ($p = 0.001$). Low ^{131}I doses (e.g., 29–50 mCi) were as effective as high doses (51–200 mCi) in controlling tumor recurrence (TR). Following ^{131}I therapy, recurrence and likelihood of cancer death were reduced by at least half.

101. (2) **Hay ID,** et al. Unilateral total lobectomy: is it sufficient surgical treatment for patients with AMES low-risk papillary thyroid carcinoma? Surgery 1998;124:958–964.

This retrospective study evaluated the outcome in 1,685 patients with PTC considered low risk by AMES criteria, initially treated during 1940 through 1991 and followed for up to 54 postoperative years (mean, 18 years). In the study, 1,656 patients (98%) had complete primary tumor resection; 634 (38%) had involvement of regional nodes. Additionally, 195 patients (12%) had undergone unilateral lobectomy; bilateral lobar resection (BLR) accounted for 1,468 (near-total, 60%; TT, 18%). Thirty-year rates for cancer-specific mortality and distant metastasis were 2% and 3%, respectively. The 20-year rates for local recurrence and nodal metastasis were 4% and 8%, respectively. Although the cancer-specific mortality or distant metastasis rates did not differ significantly between unilateral lobectomy and BLR, the 20-year rates for local recurrence and nodal metastasis were 14% and 19%, significantly higher ($p = 0.0001$) in unilateral lobectomy than the 2% and 6% rates seen after BLR.

102. (3) **Bilimoria KY,** et al. Extent of surgery affects survival for papillary thyroid cancer. Ann Surg 2007;246:375–381.

The objective of this study was to examine whether the extent of surgery affects outcomes for PTC and to determine whether a size threshold could be identified above which TT is associated with improved outcomes. From the National Cancer Data Base (1985–1998), 52,173 patients underwent surgery for PTC. Of the 52,173 patients, 43,227 (82.9%) underwent TT and 8,946 (17.1%) underwent lobectomy. For PTC less than 1 cm, extent of surgery did not impact recurrence or survival ($p = 0.24$, $p = 0.83$). For tumors greater than or equal to 1 cm, lobectomy resulted in higher risk of recurrence and death ($p = 0.04$, $p = 0.009$). The results of this study demonstrate that TT results in lower recurrence rates and improved survival for PTC greater than or equal to 1.0 cm compared with lobectomy.

103. (3) **Katoh R,** et al. Multiple thyroid involvement (intraglandular metastasis) in papillary thyroid carcinoma: A clinicopathologic study of 105 consecutive patients. Cancer 1992;70:1585–1590.

Whole thyroids resected from 105 nonselected, consecutive patients were sectioned at 2- to 3-mm intervals and histologically reviewed. Intraglandular cancer foci, other than the tumor regarded as the primary focus, were demonstrated in 78% of patients. These small foci were distributed around the primary lesion and were also found frequently (61%) in the opposite lobe as bilateral disease. In the opposite lobe, a similar incidence (~30%) of disease was seen.

Radioiodine Remnant Ablation

104. (2) **Mazzaferri EL.** Thyroid remnant ^{131}I ablation for papillary and follicular thyroid carcinoma. Thyroid 1997;7:265–271.

This study compared outcomes in 1,004 patients with differentiated thyroid cancer and no apparent residual tumor after initial thyroidectomy who underwent remnant ablation with ^{131}I ($n = 151$) with outcomes in those who were either treated with thyroid hormone alone ($n = 755$) or given no postoperative medical therapy ($n = 98$). TR and cancer deaths were lower ($p < 0.001$), and fewer patients had distant metastases ($p < 0.002$) after remnant ablation than after other forms of treatment, an effect observed only in patients with primary tumors of 1.5 cm or larger. Cancer recurrence was influenced by absence of CLN metastases (hazard ratio [HR], 0.8), tumor stage (HR, 1.8), and treatment of the thyroid remnant (HR, 0.9); cancer-specific death rates were independently affected by age (HR, 13.3), recurrence of cancer (HR, 16.6), time-to-treatment (HR, 3.5), thyroid remnant ablation (HR, 0.5), and tumor stage (HR, 2.3).

105. (2) **Hay ID,** et al. Papillary thyroid carcinoma managed at the Mayo Clinic during six decades (1940–1999): Temporal trends in initial therapy and long-term outcome in 2,444 consecutively treated patients. World J Surgery 2002;26:879–885.

In this retrospective cohort, details of the initial presentation, therapy, and outcome of 2,444 PTC patients consecutively treated during 1940 to 1999 were recorded in a computerized database. Patients were followed for more than 43,000 patient-years. The 25-year rates for Cause Specific Mortality (CSM) and TR were 5% and 14%, respectively. Temporal trends were analyzed for six decades. During the six decades, the proportion with initial MACIS (distant Metastasis, patient Age, Completeness of resection, local Invasion, and tumor Size) scores less than 6 were 77%, 82%, 84%, 86%, 85%, and 82%, respectively ($p = 0.06$). Lobectomy accounted for 70% of initial procedures during 1940 to 1949 and 22% during 1950 to 1959; during 1960 to 1999 BLR accounted for 91% of surgeries ($p < 0.001$). RRA after BLR was performed during 1950 to 1969 in 3% but increased to 18%, 57%, and 46% in successive decades ($p < 0.001$). The 40-year rates for CSM and TR during 1940 to 1949 were significantly higher ($p = 0.002$) than during 1950 to 1999. During the last 50 years, the 10-year CSM and TR rates for the 2,286 cases did not significantly change with successive decades. Moreover, the 10-year rates for CSM and TR were not significantly improved during the last five decades of the study. Increasing use of RRA has not improved the already excellent outcome, achieved before 1970, in low-risk (MACIS < 6) PTC patients managed by near-TT and conservative nodal excision.

106. (1) **Sawka AM,** et al. An updated systematic review and commentary examining the effectiveness of radioactive iodine remnant ablation in well-differentiated thyroid cancer. Endocrinol Metab Clin North Am 2008;37:457–480.

RAI remnant ablation (RRA) is used to destroy residual normal thyroid tissue after complete gross surgical resection of papillary or follicular thyroid cancer. The article updates a prior systematic review of the literature to determine whether RRA decreases the risk of thyroid cancer–related death or recurrence at 10 years after initial surgery, including data from 28 studies. No long-term randomized trials were identified, so the review is limited to observational studies. The incremental benefit of RRA in low-risk patients with well-differentiated thyroid cancer after total or near-TT who are receiving THST remains unclear.

LT4 Suppressive Therapy

107. (2) **Cooper DS,** et al. Thyrotropin suppression and disease progression in patients with differentiated thyroid cancer: Results from the National Thyroid Cancer Treatment Cooperative Registry. Thyroid 1998;8:737–744.

A cohort of 683 patients (617 with PTC and 66 with FTC) were observed during annual follow-up for a median of 4.5 years. Cancer status was defined as no residual disease; progressive disease at any follow-up time; or death from thyroid cancer. A mean TSH score was calculated for each patient by averaging all available TSH values, where 1 = undetectable, 2 = subnormal, 3 = normal, and 4 = elevated TSH. The degree of TSH suppression did not differ between PTC and FTC patients but was higher in PTC patients who were initially classified as being at higher risk for recurrence. For all stages of PTC, disease stage, patient age, and ^{131}I therapy predicted disease progression, but TSH score category did not. TSH score category independently predicted disease progression in high-risk patients but was no longer significant when ^{131}I therapy was included in the model.

108. (2) **Pujol P,** et al. Degree of thyrotropin suppression as a prognostic determinant in differentiated thyroid cancer. J Clin Endocrinol Metab 1996;81:4318–4323.

One hundred forty-one patients who underwent LT4 therapy after thyroidectomy were observed on a follow-up basis from 1970 to 1993. Patients received LT4 (mean dose, 2.6 μg/kg/d). TSH suppression was evaluated by TRH stimulation test until 1986, thereafter by a sensitive TSH assay. RFS was longer in the group with constantly suppressed TSH (all TSH values, <0.05 mU/l) than in the group with nonsuppressed TSH (all TSH values, >1 mU/l; $p < 0.01$). The level of TSH suppression was analyzed by studying the percentage of undetectable TSH values (<0.05 mU/l) during follow-up. Patients with greater TSH suppression (>90% of undetectable TSH values) had a trend toward a longer RFS ($p = 0.14$), whereas patients with less TSH suppression (<10% of undetectable TSH values) had a shorter RFS ($p < 0.01$). In multivariate analysis, the degree of TSH suppression independently predicted RFS ($p = 0.02$).

109. (1) **McGriff NJ,** et al. Effects of thyroid hormone suppression therapy on adverse clinical outcomes in thyroid cancer. Ann Med 2002;34:554–564.

Meta-analysis to evaluate the effect of THST on clinical outcomes of papillary and/or follicular thyroid cancer (ThyCa). By using a quantitative research synthesis approach in a cumulative ThyrCa cohort, the authors evaluated the effect of THST on the likelihood of major adverse clinical events (disease progression/recurrence and death). A total of 28 clinical trials published during the period 1934 to 2001 were identified; only 10 were amenable to meta-analysis. Causality was assessed by Hill criteria. Out of 4,174 patients with ThyrCa, 2,880 (69%) were reported as being on THST. Meta-analysis showed that the group of patients who received THST had a decreased risk of major adverse clinical events (RR = 0.73; CI = 0.60–0.88; $p < 0.05$). Further, 15/17 interpretable studies showed either a "likely" or "questionable" beneficial effect of THST. Assessment of causality between TSHT and reduction of major adverse clinical events suggested a probable association. The authors conclude that THST appears justified in ThyrCa patients following initial therapy. As most primary studies were imperfect, future research will better define the effect of THST upon ThyrCa clinical outcomes.

110. (4) **Sherman SI.** Tyrosine kinase inhibitors and the thyroid. Best Practice Res Clin Endocrinol Metab 2009;23:713–722.

Excellent review on efficacy, response rates, and adverse effects of protein TKIs as novel therapeutic agents for patients with DTC and MTC unresponsive to conventional therapy.

111. (3) **Wells SA,** et al. Vandetanib for the treatment of patients with locally advanced or metastatic hereditary medullary thyroid cancer. J Clin Oncol 2010;28:767–772.

This open-label, phase II study assessed the efficacy of vandetanib; a selective oral inhibitor of RET, vascular endothelial growth factor receptor; and epidermal growth factor receptor signaling in patients with advanced hereditary MTC. Patients with unresectable locally advanced or metastatic hereditary MTC received initial treatment with once-daily oral vandetanib 300 mg. The dose was adjusted additionally in some patients on the basis of observed toxicity until disease progression or any other withdrawal criterion was met.

The primary assessment was objective tumor response (by RECIST [Response Evaluation Criteria in Solid Tumors]). Thirty patients received initial treatment with vandetanib 300 mg/d. On the basis of investigator assessments, 20% of patients experienced a confirmed partial response (median duration of response, 10.2 months). An additional 53% of patients experienced stable disease at greater than or equal to 24 weeks, which yielded a disease control rate of 73%. In 24 patients, serum calcitonin levels showed a greater than or equal to 50% from baseline that was maintained for at least 4 weeks; 16 patients showed a similar reduction in serum CEA levels. The most common adverse events were diarrhea (70%), rash (67%), fatigue (63%), and nausea (63%).

Euthyroid Sick Syndrome

112. (4) **Chopra IJ.** Euthyroid sick syndrome: Is it a misnomer? J Clin Endocrinol Metab 1997;82:329–334.

This article covers the concept and laboratory abnormalities of the ESS, its pathogenesis, clinical significance, and difficulties surrounding the diagnosis of thyroid disease in patients affected by systemic nonthyroidal illness. It also reviews the evidence for and against thyroid hormone replacement in this condition.

113. (2) **Slag MF,** et al. Hypothyroxinemia in critically ill patients as a predictor of high mortality. JAMA 1981;245:43–45.

This prospective cohort study evaluated 86 critically ill patients admitted to an intensive care unit. Exclusion criteria included expected poor outcome (concurrent malignancy or so-called DNR status), chronic renal failure, transfusion of blood products in the previous 48 hours, simple arrhythmias, drug overdose, and known thyroid disease or current treatment thyroid hormone. Patients had blood specimens obtained within the first 24 hours of admission to the intensive care unit, and assays of thyroid function tests were performed (T4, T3, TBG, TSH, T3 resin uptake, rT3 and FT4 index calculated). Thirty-five clinically euthyroid subjects from an outpatient clinic were used as controls (33 men and 2 women; age range, 21–74 years). Of these patients, 22% had a low T4 level (8% <3 mg/dl and 14% 3–5 mg/dl), and of these, 30% also had a low FT4 index. The overall mortality rate was 25%. Low T4 values were highly correlated with mortality. An initial T4 level less than 3 mg/dl correlated with 84% mortality ($p < 0.01$), and the mortality rate decreased as T4 levels increased. Of patients with a low T3 level, 44% died during the hospital admission. Neither T3 nor rT3 levels correlated with or predicted mortality.

Treatment

Thyroid Hormone Supplementation

114. (1) **Mullis-Jansson SL,** et al. A randomized double-blind study of the effect of triiodothyronine on cardiac function and morbidity after coronary bypass surgery. J Thorac Cardiovasc Surg 1999;117:1128–1134.

This double-blind, randomized, placebo-controlled study was undertaken to define the effect of T3 on hemodynamics and outcome after coronary artery bypass grafting in 170 patients undergoing elective coronary artery bypass grafting. Intravenous T3 (0.4-mg/kg bolus plus 0.1-mg/kg infusion over 6 hours) or placebo was administered. Patients receiving T3 had higher cardiac index, lower inotropic requirements, and incidence of postoperative myocardial ischemia (4% vs. 18%; $p = 0.007$) and pacemaker dependence (14% vs. 25%; $p = 0.013$). Seven patients in the placebo required postoperative mechanical assistance compared with none in the T3 group ($p = 0.01$).

115. (1) **Bennet-Guerrero E,** et al. Cardiovascular effects of intravenous triiodothyronine in patients undergoing coronary artery bypass graft surgery: A randomized, double-blind, placebo-controlled trial. Duke T3 Study Group. JAMA 1996;275:687–692.

This randomized, double-blind, placebo-controlled trial evaluated whether T3 administration improves hemodynamic variables and decreases inotropic drug requirements in 211 patients undergoing coronary artery surgery at high risk for requiring inotropic drug support. Treatment consisted of T3 infusion (0.8 mg/kg IV followed by 0.12 mg/kg/h for 6 hours), dopamine (positive control, 5 µg/kg/min for 6 hours), or placebo. FT3 serum levels decreased significantly during cardiopulmonary bypass in all groups and increased to twice normal range ($p < 0.001$) after initiation of T3. T3 therapy increased heart rate ($p < 0.001$) but did not change hemodynamic variables or inotropic drug requirements.

116. (1) **Kaptein EM,** et al. Clinical review: Thyroid hormone therapy for postoperative nonthyroidal illnesses: a systematic review and synthesis. J Clin Endocrinol Metab 2010;95:4526–4534.

Systematic review evaluating effects and risks of postoperative T3 therapy in adults. Electronic databases and reference lists through March 2010 were searched, and studies with comparable control groups comparing T3 to placebo therapy in RCT were selected. Data were abstracted from 14 RCT (13 cardiac surgeries and one renal transplantation). In seven

studies, intravenous (IV) T3 was given in high doses (0.175–0.333 g/kg/h) for 6–9 hours), in four studies IV T3 was given in low doses (0.0275–0.0333 g/kg/h for 14–24 hours), and in three studies T3 was given orally in variable doses and durations. Both high- and low-dose IV T3 therapy increased cardiac index after coronary artery bypass surgery. Mortality was not significantly altered by high-dose IV T3 therapy and could not be assessed for low-dose IV or oral T3. Effects on systemic vascular resistance, heart rate, pulmonary capillary wedge pressure, new onset atrial fibrillation, inotrope use, serum TSH and T4 were inconclusive. The numbers of usable unique studies and group sizes were small, the duration of T3 therapy was short, and dosages and routes of administration varied.

3

Adrenal Disorders

Dana Erickson and Steven A. De Jong

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EVALUATION OF ADRENAL FUNCTION

Evaluation of Glucocorticoid Function

Cortisol

Normal production of cortisol by adrenal glands has diurnal variation. This fact, along with variations of "normal values" in multiple commercially available laboratory cortisol assays, explains the difficulties with diagnosis of adrenal pathology based on a single cortisol value. In general, a morning plasma cortisol less than 3 μg/dl is associated with high probability of adrenal insufficiency [1]. Basal serum cortisol may be used in assessment of the hypothalamic–pituitary–adrenal (HPA) axis. Meta-analysis of 12 studies showed basal cortisol less than 5 μg/dl to predict HPA axis insufficiency, values more than 13 μg/dl predicted normal function [2]. A midnight cortisol value of more than 7.5 μg/dl is useful for diagnosis of Cushing syndrome (CS) [3]. Additional limiting factors in interpretation of cortisol assays are caused by conditions that change the concentration of cortisol-binding protein: estrogen use and critical illness. In these instances, measurements of plasma free cortisol might be more appropriate [4].

Salivary cortisol reflects serum free cortisol. Various laboratory assays and collection methods reflect the need for each particular laboratory validation. This test performed late at night, late-night salivary cortisol (LNSC), appears to be particularly useful as a screening test for CS [5,6]. For the saliva collection method, particular laboratory methods have to be taken into consideration [7]. Initial studies using salivary cortisol measurements during dynamic endocrine studies and LNSC for determination of the outcome of transsphenoidal surgery (TSS) in CS are promising [8,9]. Salivary cortisol appeared to be helpful in the assessment of pituitary–adrenal axis in patients with cirrhosis and women on estrogens [10].

Twenty-four-hour urinary free cortisol (UFC) collection assay is the best single test for the diagnosis of CS (values at least 3 to 4 times normal are usually diagnostic

for CS). Normal values are laboratory dependent; generally, the use of immunoassays or newest high-performance liquid chromatography, or tandem mass spectrometry assays is recommended. The sensitivity and specificity depend on the cutoff value used for CS diagnosis (56%–100% sensitivity) [11]. The limitations of 24-hour collection include incomplete collection, medications that interfere with assay interpretation, periodic hypercortisolism, and pseudo-Cushing states. This test is not very helpful in the diagnosis of adrenal insufficiency. A systematic meta-analysis of diagnostic tests performed recently analyzed accuracy for initial screening tests for CS and UFC, late-night salivary cortisol, or 1-mg overnight dexamethasone suppression test (DST) and found similar likelihood ratios of these initial tests [12].

Adrenocorticotropic Hormone

Measurement of adrenocorticotropic hormone (ACTH) in plasma is important in the diagnosis of both adrenal insufficiency and CS. Two-site immunoradiometric assays should be generally obtained (along with serum cortisol values), and samples must be handled rapidly and precisely because of the instability of ACTH at room temperature. In general, levels of ACTH are elevated in primary adrenal insufficiency (PAI) and low or low normal in secondary adrenal insufficiency (SAI). In ACTH-dependent CS, ACTH is typically more than 20 pg/ml; in ACTH-independent CS, typically, it is below the low-normal limit of assay. Values in between need repeated testing or further dynamic evaluation.

Dynamic Adrenal Tests

Dynamic adrenal tests for glucocorticoid disorders are described under each pathologic condition (vide infra).

Evaluation of Mineralocorticoid Function

Resistant or multidrug hypertension, hypertension in a young patient, as well as spontaneous hypokalemia in a patient should raise the suspicion for primary hyperaldosteronism. Screening with simultaneous random plasma aldosterone concentration (PAC) to plasma renin activity (PRA) ratio (preferably in the morning after being upright for several hours) showing a value above 20 to 40 suggests positive screening test for primary hyperaldosteronism. Recent meta-analysis, however, raised uncertainty about the screening test characteristics and described lack of standardization [13]. Validated assays for plasma renin and aldosterone have to be used (various centers report a different positive cutoff for positive screening ratios), and medications that severely affect the ratio of measured hormones should be withdrawn. A multicenter study from Italy analyzing PAC/PRA ratios performed under different conditions showed good within-patient reproducibility [14]. A confirmatory test with sodium loading (NaCl tablet, typically 1 g tid × 3 days, or 3 days high-salt diet) and 24-hour urinary collection for aldosterone should follow (urinary aldosterone >14 μg/24 hr has sensitivity of 96% and specificity of 93% for diagnosis of hyperaldosteronism) [15]. A saline infusion test is used very rarely, and a cutoff value of 7 ng/dl for serum aldosterone at the end of infusion gave 100% specificity for diagnosis of primary hyperaldosteronism [16]. Mineralocorticoid deficiency is suspected when hyperkalemia and hyponatremia are present in appropriate clinical situations. No dynamic evaluation is recommended for mineralocorticoid deficiency.

Evaluation of Adrenal Medulla

Measurements of catecholamines and their metabolites are essential in the diagnostic evaluation of pheochromocytoma. For physiology and metabolism details, see the pheochromocytoma subchapter.

The utility of various available biochemical tests has been evaluated in various studies. The results of these tests depend on the type of assay used, proficiency, and lack of analytic interference of the particular laboratory and especially normative values for a given reference population. Plasma free fractionated metanephrines have the highest sensitivity (96%–99%) but a lower specificity (85%–89%), depending on the cutoffs a particular laboratory or study uses [17,18]. Severe stress and various medications could cause false-positive values, but dietary consumption of catecholamine-rich food products did not seem to influence results of measurements of free metabolites compared to deconjugated metabolites [19]. Total urinary metanephrines combined with fractionated free urinary catecholamines have also been reported to have a relatively high sensitivity and excellent specificity for catecholamine tumor diagnosis [20]. The threshold for positive plasma metanephrine test plays a significant role in diagnostic accuracy [21]. Urinary fractionated metanephrine use is limited by lack of specificity (69%), whereas urinary vanillylmandelic acid (VMA) assays lack sensitivity (65%) [17]. Plasma catecholamine use is limited by multiple compounding factors.

Evaluation of Adrenal Androgen Production and Congenital Adrenal Hyperplasia in Adults

Evaluation of adrenal tests for congenital adrenal hyperplasia is beyond the scope of this chapter. There are some excellent reviews available in the literature [22–24].

ADRENAL IMAGING

Imaging studies of the adrenal gland have undergone significant advancement over the past several years. While computed tomography (CT) scanning of the adrenal gland has often been the only imaging study needed in the evaluation of a patient with adrenal tumor, there are many other radiologic tools that often provide useful information to identify hyperfunctioning, metastatic, infiltrative, infectious, incidental, or primary malignant adrenal pathology. The abundant perinephric fat, as often seen in patients with CS, allows excellent visualization of the gland. Although clinical patient information and biochemical testing are the foundation of adrenal evaluation, imaging studies can confirm, visualize, and characterize adrenal pathology to direct medical or surgical intervention [25–27]. In addition, the widespread use of cross-sectional imaging has increased the detection of incidental adrenal masses, now seen in 5% to 8% of abdominal CT imaging [28]. Clinical decisions and treatment plans frequently depend on the accuracy of these imaging studies to demonstrate and distinguish benign, malignant, and metastatic features in these adrenal tumors [29].

Computed Tomography Scanning

Despite their small size, the adrenal glands are visualized in nearly 100% of patients with CT scanning. The V-shaped right adrenal gland is usually seen directly posterior to the inferior vena cava (IVC) and measures approximately $1 \times 2 \times 0.5$ cm. This gland is nearly the same width as the diaphragmatic stripe. The left adrenal gland, which has a similar size and shape, is located anterior to the upper portion of the kidney and directly adjacent to the aorta. Adrenal CT scanning remains an excellent initial study in the patient with adrenal disease, and 1 cm contiguous scans are routinely used to demonstrate the location, size, and tissue characteristics of most adrenal masses. This technique can also identify lymphadenopathy, obvious malignancy, and local invasion or distant metastasis associated with adrenal tumors [30]. Thinner scans using 3- to 5-mm slices are often necessary to detect and evaluate smaller functional tumors such as

aldosteronomas. Most pheochromocytomas or adrenal adenomas causing CS are 2 to 5 cm in diameter, whereas most aldosteronomas are 8 mm to 2 cm in size. The main limitation of CT scanning is its periodic inability to separate benign from malignant and functional from nonfunctional tumors of the adrenal. Cysts and myelolipomas are the only benign conditions readily identified with CT scanning. An adrenal lesion with a large amount of macroscopic fat is readily identified as a myelolipoma. Most smooth-walled water density adrenal lesions are cysts, but necrotic metastatic adrenal tumors can appear cystic and have higher density [27]. Benign adrenal adenomas are low density, lipid rich, and have an attenuation value of less than 10 Hounsfield units (HU) measured with the region of interest on noncontrast CT images (NCCT) [27]. For adrenal lesions with density greater than 10 HU, the use of IV contrast improves this distinction and benign adrenal adenomas often exhibit more than an absolute washout percentage of 60% measured 15 minutes after initial enhancement using standard contrast-enhanced CT (CECT) imaging of the adrenal gland [31]. A relative washout percentage, calculated when NCCT density is not available, of over 40% is consistent with benign adrenal disease [32]. Although contrast enhancement may increase accuracy, patients with suspected pheochromocytoma should undergo α-adrenergic blockade before contrast administration to eliminate the small risk of contrast agents precipitating a hypertensive crisis. Comparison to prior adrenal CT imaging remains important, as the volume and dimensions of benign adenomas are usually stable and only enlarge very gradually, if at all. Significant growth is frequently associated with malignancy, although adrenal hemorrhage can cause rapid enlargement in benign adrenal tumors [29]. Many surveillance imaging schedules exist for incidentally detected presumed benign adrenal tumors. While some believe this may be excessive, a reliable recommendation is for 6-month, 1-, 2-, and 3-year follow-up cross-sectional imaging to confirm lesion stability and exclude adrenal cortical malignancy. Primary adrenal malignancy should be considered in large adrenal masses with calcification, necrosis, or hemorrhage. CT of the adrenal gland has reported sensitivity, specificity, and accuracy rates of 84%, 98%, and 90%, respectively [4,11]. Percutaneous biopsy of the adrenal gland is rarely indicated but can be safely performed by using CT guidance techniques. The left adrenal gland is usually more difficult to access for biopsy with this technique because of its posterior location [33].

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is gaining widespread acceptance as the initial study in the evaluation of adrenal masses because of its superb soft tissue contrast, natural enhancement of certain pathologic adrenal masses, and the lack of ionizing radiation. MRI characterizes adrenal tumors by their signal characteristics on different pulse sequences and by their enhancement characteristics. It also allows multiplanar imaging to depict the relation between the adrenal mass and the kidney [34]. MRI accurately identifies benign adrenal adenomas, myelolipomas, adrenal cysts, malignant or metastatic adrenal tumors, and pheochromocytomas and generally augments information obtained with CT [35]. MRI reliably distinguishes between adenoma and metastasis in most cases and allows accurate oncologic staging, limited adrenal biopsies, and initiation of appropriate treatment regimens in the affected patient population. Chemical-shift techniques using breath-hold T_1-weighted gradient echo (GRE) images can rapidly and reliably identify benign adrenal adenomas through the accurate detection of their characteristic high intracellular lipid content [34,36]. Chemical-shift MRI offers little advantage over NCCT, but some continue to recommend this technique to differentiate lipid-rich benign adenomas from their

lipid-poor indeterminate or malignant counterparts [27]. Normal adrenal glands and adrenal tumors larger than 1 cm in diameter can be visualized in more than 90% of patients with these images, but MRI is not able to distinguish functional from nonfunctional cortical adenomas of the adrenal. T_2-weighted images, however, can demonstrate unique signal intensities. Hyperintense T_2-weighted images suggest the presence of pheochromocytoma, and MRI can also be useful in locating extra-adrenal pheochromocytomas. The MRI signal intensity of adrenal cortical carcinomas is variable, and they generally are heterogeneous on T_1- and T_2-weighted images. These tumors often appear as large, necrotic, poorly marginated retroperitoneal masses of uncertain origin where MRI fails to identify a normal ipsilateral adrenal gland [37]. These aggressive neoplasms often invade into the renal vein or IVC, and this venous extension can also be demonstrated on MRI. MRI is also an attractive imaging modality for children and pregnant patients with adrenal disease because of its lack of ionizing radiation.

Adrenal Cortical Scintigraphy

Hormone production in the adrenal cortex begins with cholesterol, and several radiolabeled cholesterol analogs have been developed to allow localization and functional information regarding adrenal cortical tumors. The only one currently approved for use in the United States is [^{131}I]-6β-iodomethylnorcholesterol (NP-59). Unfortunately, NP-59 scanning has been largely abandoned as it is difficult to obtain, expensive, time consuming, and involves significant radiation exposure to the patient. The material, however, is safe to administer, and the accuracy rate of NP-59 to identify and distinguish correctly a Cushing adrenal adenoma or an aldosteronoma from bilateral adrenal hyperplasia approaches 90% [38]. Detection of aldosteronomas with NP-59 requires discontinuation of diuretic and antihypertensive medication, and accuracy rates are increased if the patients are pretreated with dexamethasone.

Adrenal Medullary Scintigraphy

Metaiodobenzylguanidine (MIBG), a radiolabeled derivative of guanethidine with no pharmacologic effect, was developed in 1980. It is the most frequently used substance to image the adrenal medulla and other sympathetic tissues. It is incorporated into sympathetic nerve cells as a catecholamine precursor. [^{131}I] MIBG is the most commonly used isotope, but recent studies suggest that ^{123}I is more accurate with less radiation exposure to the patient. Single-photon emission computed tomography technology may also improve the sensitivity and accuracy of this imaging tool. MIBG scanning is diagnostic for neoplasms producing excess catecholamine and has successfully detected pheochromocytomas, neuroblastomas, and other neuroendocrine tumors such as paragangliomas, carcinoid tumors, and medullary carcinomas of the thyroid. The most common role for MIBG is in patients with a biochemical diagnosis of pheochromocytoma and normal conventional adrenal imaging studies. MIBG can identify paragangliomas and metastatic pheochromocytomas to guide further imaging. The sensitivity and specificity of MIBG scanning for pheochromocytoma and neuroblastoma are between 80% and 100%. An alternative to MIBG is radiolabeled octreotide [^{111}I(indium)]-DTPA (diethylenetriaminepenta-acetate) octreotide, which can detect paragangliomas and neuroendocrine tumors containing cell-surface receptors for somatostatin [39]. Unfortunately, this imaging modality is only 30% sensitive [40]. The use of MIBG may be decreasing with the adoption of positron emission tomography (PET) scanning, which often demonstrates increased FDG activity [41].

Positron Emission Tomography

Several different radiopharmaceuticals can detect increased cellular activity in hyperfunctional adrenal states more specifically than does conventional imaging. These agents can also target specific adrenal enzymes that are expressed in adrenal tumor cells. As an example, [^{18}F]fluorodopamine PET scanning allows tumor visualization within minutes of injection of the imaging agent, and spatial resolution is excellent. Malignant cells are frequently glucose avid, and PET scanning with the glucose analog ^{18}F-fluoro-deoxyglucose (^{18}F FDG) is effective in differentiating benign from malignant and metastatic adrenal lesions with 97% sensitivity and 91% specificity [42,43]. PET scanning also correctly localizes adrenal and extra-adrenal pheochromocytomas that lack the ability to concentrate MIBG [44,45]. PET imaging is now frequently combined with CT imaging (CT/PET) to assess both the gross appearance of the lesion and its metabolic activity [27].

Adrenal Vein Sampling

Adrenal vein sampling is useful in patients with functional tumors of the adrenal glands such as in patients with CS or primary hyperaldosteronism. These patients have normal or equivocal findings on CT, MRI, or adrenal scintigraphy, and these imaging studies cannot distinguish between a unilateral aldosteronoma requiring adrenalectomy from bilateral adrenal hyperplasia treated medically [46]. Although the left adrenal vein is accessible in nearly all patients, the right adrenal vein can be more difficult to cannulate. Patients with primary hyperaldosteronism receive an infusion of cosyntropin, and blood from both adrenal veins and the distal IVC is measured for both aldosterone and cortisol. Adrenal vein cortisol should be five times greater than IVC cortisol to verify the position of the venous catheter in the adrenal vein. The ratios of aldosterone to cortisol for both adrenal veins are compared, and a ratio of 4:1 or greater reliably identifies a small unilateral aldosteronomas, whereas a ratio of less than 3:1 usually indicates bilateral adrenal hyperplasia [47]. Selective venous sampling in patients with CS is performed in a similar manner without the infusion of cosyntropin. Cortisol levels from both adrenal veins and the IVC are compared to distinguish between bilateral adrenal hyperplasia and adrenal adenoma in patients with CS.

PRIMARY HYPERALDOSTERONISM

Definition and Etiology

Primary hyperaldosteronism is the excessive autonomous adrenal secretion of aldosterone, resulting in elevation of PAC and suppression of PRA. While the exact cause is unknown, this syndrome results in a rare form of surgically correctable hypertension, polyuria, weakness, hypokalemia, sodium retention, and mild metabolic alkalosis. A small, benign, unilateral, aldosterone-producing adrenal tumor, first described by Jerome Conn in 1955, was historically the most common cause of primary hyperaldosteronism in 70% of patients. Currently though, the contemporary incidence of idiopathic bilateral macronodular or micronodular hyperplasia of the adrenal cortex causing primary hyperaldosteronism has increased to over 50%, largely due to widespread screening of hypertensive patient populations [48,49]. Other far less common causes of primary hyperaldosteronism include unilateral primary adrenal hyperplasia detected by adrenal venous sampling (AVS), glucocorticoid-suppressible hyperaldosteronism, a rare familial form of hypertension that affects 1% to 3% of patients with primary hyperaldosteronism [50], and aldosterone-producing adrenal carcinoma [51].

Epidemiology

The prevalence of primary hyperaldosteronism in unselected patients with hypertension is 0.5% to 2%, but centers routinely obtaining PAC/PRA ratios detected primary hyperaldosteronism in 8% to 15% of their hypertensive patients, representing a 10-fold increase in this diagnosis [52]. Age at diagnosis ranges between 30 and 60 years, and about 1% of all adrenal masses discovered incidentally are found to be aldosterone-producing adrenal adenomas. Aldosteronomas occur more commonly in female patients, by a 2:1 ratio, and are rare in children. Patients with aldosteronomas tend to be younger, have more severe hypertension and hypokalemia, have higher urine and serum aldosterone levels, and respond better to spironolactone than patients with bilateral adrenal disease. Bilateral idiopathic adrenal hyperplasia causing primary hyperaldosteronism is more common in men and usually appears in patients at an older age when compared to aldosteronoma. High blood pressure is present, but this sign is a common medical problem and is not sufficiently specific to identify this endocrinopathy. Although hypertension in these patients is often of moderate severity, multiple medical regimens to control blood pressure are usually unsuccessful, causing the diagnosis of primary hyperaldosteronism to be considered [50].

Pathophysiology

Aldosterone is the final product in the biosynthesis of mineralocorticoids produced from the zona glomerulosa of the adrenal cortex. Factors stimulating the synthesis and release of aldosterone include angiotensin II, potassium, ACTH, and decreased renal perfusion or circulating blood volume. The clinical manifestations of primary hyperaldosteronism arise from the autonomous production of aldosterone, causing altered sodium and potassium homeostasis. Aldosterone normally enhances the reabsorption of sodium from the distal renal tubules in exchange for potassium and hydrogen excretion. Excessive aldosterone secretion leads to sodium and water retention and increased potassium and hydrogen excretion. The result is volume expansion and hypertension, suppressed PRA, hypokalemia, and metabolic alkalosis [48]. Serum sodium levels usually remain normal because of a parallel increase in the water content of the blood, but mild hypernatremia can be present. Hypokalemia appears to be responsible for most of the clinical symptoms of primary hyperaldosteronism, such as proximal muscle weakness and cramps, polyuria, polydipsia, nocturia, headache, and fatigue.

Diagnosis

Unlike most endocrine disorders, primary hyperaldosteronism does not have characteristic symptoms or signs, but this disorder should be considered in all patients with hypertension, unprovoked hypokalemia, and metabolic alkalosis. The use of antihypertensive medications that specifically block aldosterone secretion, such as spironolactone and other similar diuretics, must be stopped for 4 to 6 weeks before biochemical testing. Screening studies such as measurement of PRA, PAC, and potassium levels, along with a 24-hour urine collection for aldosterone, potassium, and sodium, should begin the evaluation. Most patients with primary hyperaldosteronism have a serum potassium level less than 4.0 mEq/l, and some can range from 2.5 to 3.5 mEq/l at the time of clinical presentation [40,50]. Recent studies, however, describe a rising incidence of normokalemia seen in as high as two-thirds of patients with early primary hyperaldosteronism found by screening laboratory studies performed on hypertensive patients [53]. Despite hypokalemia and a total body deficit of potassium, the 24-hour urine collection for potassium demonstrates inappropriate kaliuresis. Diuretic-induced hypokalemia that does not respond to potassium replacement also suggests the presence of primary hyperaldosteronism.

Plasma aldosterone levels can be elevated or normal, but the PRA is invariably suppressed. Low PRA excludes the presence of secondary hyperaldosteronism, characterized by increased renin and aldosterone levels, and resulting from renal artery stenosis, cirrhosis, intravascular volume loss, congestive heart failure, and other disorders that decrease renal perfusion. Plasma aldosterone levels usually exceed 15 to 30 ng/l, and PRA is usually less than 1 ng/l. A ratio of plasma aldosterone to PRA that exceeds 30 to 50 is highly suggestive of excess endogenous aldosterone production [48,50]. A PAC/PRA ratio of 20:1 along with a PAC greater than 15 ng/dl was also found to be highly sensitive in establishing the diagnosis [54].

Oral or intravenous sodium chloride administration may be necessary in some hypertensive patients where the distinction between primary and secondary hyperaldosteronism is less clear. Primary autonomous aldosterone secretion is confirmed when PAC was greater than 5 to 10 ng/dl after a 2-l saline infusion over 4 hours or urinary aldosterone levels were greater than 12 ng/dl after liberal oral intake of high-sodium-content foods over 3 to 4 days [52]. In addition, the inability to reduce plasma aldosterone levels and increase PRA after the administration of captopril, an angiotensin-converting enzyme (ACE) inhibitor, also suggests primary hyperaldosteronism [50].

After the diagnosis of primary hyperaldosteronism is confirmed, the main cause of this syndrome, either unilateral adrenal adenoma or idiopathic bilateral adrenal hyperplasia, must be determined because of significant treatment implications [55]. Postural testing can be used to make this distinction because unilateral aldosterone-producing adrenal adenomas are unresponsive to the effects of angiotensin II. Plasma levels of aldosterone are measured in patients assuming a supine position and then again after 4 hours of standing. Angiotensin II and PRA increase in the standing position, but patients with aldosterone-producing adrenal adenomas have no increase in their aldosterone levels during this test. Conversely, aldosterone levels in patients with idiopathic bilateral adrenal hyperplasia usually increase. Postural testing can correctly differentiate between unilateral and bilateral adrenal disease in 75% to 85% of patients with primary hyperaldosteronism [48,55,56]. CT scanning of the adrenal glands has largely replaced postural testing in many centers as the initial study of choice to identify the aldosteronoma, but postural testing is helpful in equivocal cases or when a nonfunctional adrenal adenoma is suspected. Measurement of 18-hydrocorticosterone is not uniformly available but can also distinguish adrenal adenoma from bilateral adrenal hyperplasia. Plasma levels of 18-hydrocorticosterone greater than 100 ng/dl are indicative of unilateral adrenal adenoma with a sensitivity of 60% to 85% [57], but postural testing and serum 18-hydrocorticosterone levels alone cannot lateralize the disease process or localize the aldosteronoma [58].

Imaging of the adrenal glands, after diagnostic confirmation of primary hyperaldosteronism, is best performed with enhanced high-resolution CT scanning of both adrenal glands, which has an 80% to 90% sensitivity rate in detecting aldosteronomas. This technique, however, can also detect tiny adrenal nodules or adrenal limb thickening that may or may not have any clinical significance. Aldosteronomas are usually 0.5 to 2 cm in diameter and require imaging in 3-mm increments rather than the conventional 1-cm CT sections. It is important to visualize the contralateral adrenal gland adequately because enlargement of both glands may suggest idiopathic bilateral adrenal hyperplasia. The sensitivity of MRI is equal to that of CT scanning for these patients [50].

Patients under 40 years of age with biochemically confirmed primary hyperaldosteronism and CT imaging demonstrating a solitary adrenal adenoma larger

than 1 cm with rapid contrast washout and a normal contralateral adrenal gland can undergo surgical resection with no further testing. Older surgical candidates, however, with primary hyperaldosteronism and either no adrenal mass, bilateral adrenal masses, an adrenal microadenoma, or equivocal findings on CT or MRI should undergo adrenal vein sampling for aldosterone and cortisol levels to determine the origin of the primary hyperaldosteronism. Adrenal vein sampling for aldosterone has a diagnostic sensitivity of 96% but does require significant technical expertise, as the short right adrenal vein can be challenging to cannulate. Technical failure rates range from 5% to 30%. ACTH is administered, and aldosterone and cortisol levels are measured from both adrenal veins and the IVC. An adrenal vein/IVC cortisol ratio of 5:1 ensures proper placement of the catheter into the respective adrenal vein. A unilateral aldosterone-producing adenoma (APA) produces a ratio of aldosterone to cortisol that is four to five times greater than that of the opposite side [58]. Bilateral adrenal disease reveals bilateral elevation of this ratio and no appreciable gradient. One study compared CT and adrenal vein sampling in 24 patients with primary hyperaldosteronism [59]. CT led to diagnosis of unilateral adenoma in 19 patients and hyperplasia in seven. After AVS, unilateral adenoma was diagnosed in 22 patients. Of the seven patients with bilateral nodules, AVS correctly identified the unilateral adenoma in six. Other studies [60] found that CT imaging without AVS would have inappropriately excluded 22% of the patient population from surgical consideration and exposed 25% of patients to unnecessary or inappropriate adrenalectomy.

Iodocholesterol scanning with [6β-^{131}I]iodomethyl-19-norcholesterol (NP-59) after dexamethasone suppression is a less-used imaging study to differentiate adenoma from hyperplasia. This study has a reported sensitivity of 88% and can identify unilateral uptake in larger adrenal aldosteronomas and bilateral uptake in adrenal hyperplasia [48,50]. In a study of 41 patients who were examined by using CT and iodocholesterol scanning with NP-59 after dexamethasone suppression, scintigraphy correctly identified bilateral and unilateral lesions in 92% of cases compared with 58% by CT [61]. Aldosterone-producing adrenal carcinoma often demonstrates no uptake on adrenal scintigraphy [51]. Unfortunately, this study depends heavily on the size of the adenoma, and its declining use is limited by the availability of the radioisotope.

Treatment

Unilateral adrenal aldosteronomas are treated with laparoscopic or open adrenalectomy [62]. Adrenal resection is performed after a 1- to 2-week course of spironolactone at 25 to 400 mg/d in divided doses to correct the hypokalemia and other associated volume and metabolic derangements. Adrenalectomy is likely to be successful if the patient's hypertension is efficiently controlled with preoperative spironolactone [63]. The intra-abdominal or posterior retroperitoneal laparoscopic approach is the method of choice because of fewer wound complications, less patient discomfort, shorter hospitalizations, and a more rapid return to work and normal activity. Visual examination of the sectioned adrenal gland reveals a solitary bright golden yellow tumor with well-defined borders arising from the otherwise normal adrenal parenchyma. Spironolactone should be discontinued after unilateral adrenalectomy, and potassium supplements can be rapidly tapered and then stopped. Resolution of preoperative hypokalemia usually occurs within 5 to 7 days of adrenalectomy in 95% of patients, and cure of hypertension over several months is expected in 70% to 80% of patients with normal renal function [62,64]. The remaining 20% to 30% of patients usually experience improvement in blood pressure control, and they often require

fewer antihypertensive medications at lower doses after adrenalectomy. Both recurrence of primary hyperaldosteronism incidence of adrenal insufficiency after unilateral adrenalectomy for aldosteronoma is rare.

Hypertension and hypokalemia in patients with idiopathic bilateral adrenal hyperplasia are best treated medically with potassium-sparing diuretic agents such as spironolactone, amiloride, and other antihypertensive agents. These medications can be associated with gynecomastia, menstrual irregularities, and impotence [50], but the use of eplerenone, a more selective aldosterone antagonist, may be associated with fewer undesirable side effects [65]. Hypertension in these patients responds poorly to bilateral adrenalectomy, which invariably leads to hypocortisolism, otherwise known as Addison disease. Aldosterone-producing adrenal carcinomas occur in 1% of patients with primary hyperaldosteronism and have an overall 5-year survival rate of 35%. These tumors are often large with aggressive invasive features and require open adrenalectomy for complete resection or debulking [51].

CUSHING SYNDROME

The constellation of clinical features that result from persistent, inappropriate elevation of glucocorticoids is described as CS. The incidence of endogenous CS is low, 0.7 to 2.4 per million population; however, recent studies suggest perhaps a higher incidence in a patient population with poorly controlled diabetes or osteoporosis [66,67] in some but not all studies [68].

Etiology and Pathogenesis

Exogenous administration of glucocorticoids (iatrogenic or factitious) is the most common cause of CS. Approximately 80% of patients with endogenous CS have ACTH-dependent disease, most frequently caused by pituitary microadenomas (i.e., Cushing disease; see Chapter 1) [69]. Overproduction of ACTH in ACTH-dependent Cushing may also be due to ectopic overproduction of ACTH or corticotropin-releasing hormone (CRH), caused by certain malignancies (Table 3.1) [70]. The excessive ACTH or CRH production leads to overproduction of cortisol by adrenal glands. In ACTH-independent CS (15%–20% of endogenous causes), autonomous increase in cortisol production by adrenal glands is found, resulting in suppression of ACTH. The etiology of this autonomous cortisol overproduction is represented by: adrenal adenomas, adrenal carcinomas, bilateral or unilateral macronodular adrenal hyperplasia, and micronodular adrenal hyperplasia. The expression of certain ectopic promiscuous receptors (gastric inhibitory polypeptide, vasopressin, β-adrenergic receptors, serotonin, and luteinizing hormone receptors) in adrenocortical cells explains some of the causes of macronodular adrenal hyperplasia [71]. Certain conditions such as affective disorders, stress, and obesity can lead to mild elevations in plasma or urinary cortisol levels, the so-called pseudo-Cushing state. The entity of subclinical CS (SCS) is described in the section on adrenal incidentalomas.

Clinical Features

The clinical manifestations of hypercortisolism are common to all forms of CS and include hypertension; central obesity; diabetes mellitus [72]; acne; androgenic hirsutism; signs of protein catabolism such as myopathy, osteopenia, or osteoporosis; cutaneous lesions (i.e., wide violaceous striae, tinea versicolor, verrucous vulgaris, ecchymosis); hyperpigmentation; and psychiatric manifestations (depression, cognition, and vegetative function). Increased thrombotic events

Table 3.1. Causes of Cushing Syndrome

Exogenous: oral, injectable, inhalational, topical, glucocorticoids
Endogenous
ACTH dependent
Pituitary ACTH production: Cushing disease
Ectopic ACTH production: Small cell lung carcinoma
Small cell lung Ca
Carcinoid
Pancreatic cancer
Pheochromocytoma
Medullary thyroid carcinoma
Ectopic CRH production
ACTH independent (adrenal glucocorticoid overproduction)
Adrenal adenoma
Adrenal carcinoma
Bilateral micronodular hyperplasia
Bilateral macronodular hyperplasia

ACTH, adrenocorticotropic hormone; CRH, corticotropin-releasing hormone.

were well documented in recent meta-analysis [73].The classic features may not be present in ectopic ACTH production from malignancies, because of shorter duration of hypercortisolemia. Impaired quality of life is seen in patients with CS after remission of CS [74].

Evaluation

Diagnostic Tests

Measurement of 24-hour UFC is the most reliable screening test for CS. The sensitivity is reported to be between 56% and 100%, and the specificity varies depending on study population, assays, and laboratory cutoffs for elevation [75]. A value that is more than four times the upper limit of normal is typically considered to be indicative of CS.

Loss of circadian rhythm with high plasma cortisol level (7.5 mg/dl) between 10 p.m. and midnight is an early indicator of CS [3]. Late-night salivary cortisol testing in a total of 339 patients with CS measured by various methods, laboratories, and cutoff generation showed pooled sensitivity of 92% and specificity of 96% in a recent meta-analysis [6].

The overnight DST (dexamethasone, 1 mg PO administered at 11 p.m., followed by 8 a.m. plasma cortisol) is used as a screening test for CS [76]. Various criteria for normal suppression (traditionally <5 μg/dl or recently <1.8 μg/dl) applied to various study populations and frequently lack of matching controls influence sensitivity and specificity of the test [77]. Data regarding salivary post–1-mg dexamethasone cortisol test are very limited. A systematic meta-analysis of diagnostic tests performed recently analyzed accuracy for initial screening tests for CS and UFC, late-night salivary cortisol, or 1-mg overnight DST and found similar likelihood ratios of these initial tests [12].

In the 2-day low-dose dexamethasone test, dexamethasone, 0.5-mg tablet, is taken every 6 hours for 2 days, followed by plasma cortisol determination at 8 a.m. Normal response includes plasma cortisol level suppression to less than

5 μg/dl (or more stringent cutoff of <1.8 μg/dl) and UFC suppression below the lower limit of normal [12,76–78]. Dexamethasone—0.5 mg every 6 hours for 2 days followed 2 hours later by intravenous ovine CRH, 1 μg/kg—yields plasma cortisol of less than 1.4 to 2.5 mg/dl at 15 minutes in patients with pseudo-Cushing [79,80]. Various medications can confound interpretation of this test [81].

Baseline ACTH Level

An inappropriately normal or elevated baseline plasma ACTH level (i.e., >20 pg/ml) indicates ACTH-dependent CS. Cushing disease usually appears with ACTH levels less than 200 pg/ml, whereas ACTH levels in ectopic ACTH syndromes range from 200 to 1,000 pg/ml. A low ACTH level (typically <5 pg/ml) represents ACTH-independent CS.

High-Dose Dexamethasone Suppression

The high-dose dexamethasone suppression (HDDS) test is done to differentiate between pituitary ACTH overproduction and ectopic ACTH production and occasionally in ACTH-independent CS. Dexamethasone, 2 mg orally every 6 hours for 2 days, is followed by plasma cortisol estimation at 8 a.m. Plasma cortisol below 50% of basal values or 24-hour UFC less than 90% of basal values indicates Cushing disease [82]. Absence of response to HDDS indicates ectopic ACTH or adrenal CS. In the overnight HDDS test, a single dose of 8-mg dexamethasone is given at 11 p.m., and 8 a.m. plasma cortisol is measured the next day. The test is interpreted the same way as is standard HDDS testing. In a limited series, the sensitivity and specificity of the overnight HDDS test are similar to those of the standard HDDS test; however, a higher plasma cortisol suppression (>68%) cutoff was used for the latter [83]. Effectiveness analysis of both tests points toward the limitations of these tests by using standard criteria in interpretation [84]. Note that the pretest probability of pituitary Cushing disease is high, which limits the usefulness of these tests. In general, these tests are not used very frequently in current practice.

Invasive testing including inferior petrosal or cavernous sinus sampling (highest sensitivity and specificity), as well as CRH stimulation tests, are discussed in the section on Cushing disease in Chapter 1.

Radiologic Imaging

Thin-section CT (3-mm cuts) or MRI of the adrenal glands to look for the cause of adrenal autonomy is the next step in evaluation of patients with ACTH-independent CS. Imaging of ACTH-dependent CS is discussed in Chapter 1.

Treatment

The goal of therapy is to eradicate the cause of CS. Treatment of pituitary Cushing disease is described in Chapter 1. Optimal therapy in cases of ACTH-independent CS includes surgical removal of adrenal adenoma or carcinoma. In cases of ACTH-independent bilateral hyperplasia (micronodular or macronodular), as well as in certain cases of persistent or recurrent ACTH-dependent disease, bilateral adrenalectomy is the treatment of choice. The laparoscopic approach to surgery has reduced the surgical morbidity of adrenalectomy. The hospital stay is shorter, and complications are much less frequently encountered compared with results associated with open surgery. Mortality is reported at 0.2% [85].

Medical treatment can be used when surgery is contraindicated, if the tumor is metastatic or occult, or if surgery and radiation therapy (for pituitary disease) have failed. Medical therapy may also be used to attempt to stabilize patients preoperatively.

Medications used to reduce cortisol production are divided into several groups: those inhibiting adrenal steroidogenesis (mitotane, ketoconazole, aminoglutethimide, etomidate, and metyrapone); those acting at pituitary level (cyproheptadine, bromocriptine, cabergoline, somatostatin and analogs, valproic acid, thiazolidines short-term effect); and last, glucocorticoid-receptor antagonist (mifepristone; not commercially available yet). Ketoconazole is initiated at a dose of 200 mg three times daily and then increased to 400 mg three times daily with effective plasma cortisol reduction [86]. Liver-function test abnormalities can occur. The therapeutic effect is frequently transient. As with all of adrenal steroidogenesis inhibitors, acute adrenal insufficiency can occur; therefore, physiologic glucocorticoid replacement might be necessary. Mitotane is implemented at a dose of 0.5 to 1 g/d and increased by 0.5 to 1 g over a period of a few weeks, maximum of 10 g/d; severe gastrointestinal and neurologic side effects occur [87]. Monitoring of mitotane levels and dose adjustment is frequently advocated. The starting dose of aminoglutethimide is 500 mg/d in four divided doses, with increments every few days to a maximum of 2 g/d; it is useful as an adjunctive agent, but currently, this drug is not available in the United States [88]. Pasireotide (SOM-230), a novel somatostatin analog, is showing some promising effects in initial studies [89].

Targeted medical therapy (propranolol, leuprolide) has been reported to decrease cortisol production in selected cases of documented ectopic hormone-receptor expression in bilateral macronodular hyperplasia.

ADRENAL INCIDENTALOMA

Definition

An adrenal incidentaloma is a tumor larger than 1 cm in diameter that is discovered serendipitously during routine diagnostic imaging in the absence of symptoms or clinical findings suggestive of adrenal disease. Availability of specialized imaging techniques and the more widespread application of abdominal ultrasound, CT, and MRI has made this entity a more frequently encountered phenomenon in clinical practice. In a large series of 61,054 abdominal CT scans published by the Mayo Clinic, incidental adrenal tumors were visualized in 0.4% [90]. At autopsy, an adrenal mass is found in at least 3% of persons older than 50 years [91].

Etiology

Adrenal masses visualized on imaging studies are of various etiologies (Table 3.2). The mass has to be characterized with respect to functional hormonal status and imaging characteristics. Although most incidentally discovered adrenal masses are nonfunctional, up to 15% may be hormonally active. In a study retrospectively analyzing 1,096 cases of incidentally diagnosed adrenal tumors, 9.2% were found to be cortisol secreting, 4.2% were pheochromocytomas, and 1.6%, aldosteronomas [92]. Adrenal carcinomas are very rare in this setting, and more than 98% are larger than 4 cm.

Diagnosis

A detailed clinical history and physical examination represent the initial step in evaluation of all patients [91]. Evaluation for possible hormonal hyperfunction should follow. Screening for pheochromocytoma includes measurement of 24-hour total and fractionated urinary metanephrines combined with 24-hour urinary catecholamines or measurement of fractionated plasma free metanephrines [93,94]. The choice of a particular test could be determined by certain imaging characteristics of tumor and by the clinical context.

Table 3.2. Differential Diagnosis of Adrenal Masses

Nonfunctioning Mass	Hormonally Active Mass
Benign adrenal adenoma	Pheochromocytoma
Cyst	Primary aldosteronoma
Myelolipoma	Cushing syndrome
Neurofibroma	Masculinizing or feminizing tumors
Adenolipoma	Micro- or macronodular hyperplasia
Ganglioneuroma	Adrenocortical carcinoma
Hamartoma	Pseudoadrenal Mass
Teratoma	Renal, pancreatic, vascular, neurologic origin
Infections	
Metastatic carcinoma	
Adrenocortical carcinoma	

Screening for primary hyperaldosteronism includes measurements of the plasma aldosterone/renin ratio. The optimal biochemical definition of SCS is debatable, and various studies included patients with abnormal overnight 1-mg dexamethasone (>5 μg/dl; recommendation of NIH consensus in 2003) or 3-mg suppression test, abnormal 2-day low-dose DST (cutoffs for abnormal plasma and urinary cortisol vary), lack of diurnal variation of cortisol levels, elevated baseline urinary cortisol levels, low baseline ACTH level, or abnormal CRH stimulation test [95]. LNSC does not appear to have high diagnostic accuracy in patients with SCS and adrenal incidentaloma [96]. Over the last several years, several studies have shown that patients with SCS have metabolic abnormalities (impaired glucose tolerance, increased blood pressure, and reduced insulin sensitivity), increased cardiovascular risk factors, higher triglycerides, increased total and low-density lipoprotein (LDL) cholesterol and fibrinogen levels [97], and reduced bone mass [98]. Lastly, testing for androgen overproduction should be performed in cases of severe hirsutism.

Certain imaging characteristics are very useful for differentiating malignant and nonmalignant tumors, as described in Table 3.3. Precontrast HU on CT of less than 10 HU are typical for lipid-rich adenomas, but lipid-poor adenomas can have higher attenuation (sensitivity for detection 58% for 20 HU) [99]. Fine-needle aspiration (FNA) can distinguish adrenal tumors from extra-adrenal neoplasms; however, it cannot reliably differentiate a benign adenoma from an adrenal carcinoma. Thus, FNA should not be routinely undertaken in the evaluation of an adrenal incidentaloma, unless the index of suspicion for a malignancy outside the adrenal gland is high, and the presence of pheochromocytoma must be excluded before the procedure. Adrenal scintigraphy with iodinated cholesterol derivative (i.e., NP-59) can identify patients with functioning adrenocortical tissue; however, it has very limited availability.

Treatment

Generally, adrenal tumors larger than 4 to 6 cm should be surgically excised if no evidence of metastases from a distant source is found [90,91]. Cutoff at 4 cm had the highest sensitivity (93%) in differentiating between benign and malignant tumors in a large national survey of more than 1,000 patients [92].

Table 3.3. Characteristics of Malignant and Nonmalignant Adrenal Masses

Characteristic	Malignant	Benign
Size	Typically ≥4 cm	<4 cm
CT scan appearance	Heterogeneous Calcified, hemorrhagic	Homogeneous (low density compared with liver)
Margins	Irregular	Round, smooth
Contrast media Enhancement on CT	Marked	Low
CT imaging (HU)	>10 HU without contrast and >40 HU 30 min after contrast	<10 HU without contrast and <37 HU after contrast
MRI appearance	Hyperintense	Isointense

Nonfunctioning adenomas are virtually all cured by surgery. Hormonally active tumors as pheochromocytoma, aldosteronoma, and even nonfunctioning tumor of less than 4 cm with suspicious imaging characteristics should be surgically removed. Currently, insufficient evidence exists regarding surgical intervention in patients with SCS in the setting of adrenal incidentaloma. Retrospective case analysis of patients with SCS showed amelioration of the cardiovascular risk profile after surgical removal of an adrenal mass [97]. A recent randomized, prospective trial of patients with SCS assigned to laparoscopic adrenalectomy versus medical management showed superiority of surgical management in improvement of diabetes, hyperlipidemia, and obesity without improvement in bone parameters [100]. Results of meta-analysis of published studies of open adrenalectomy with the laparoscopic procedure for benign disease illustrate the advantages of the latter [101]. In cases of adrenal cancer, open adrenalectomy appears to be the procedure of choice, although reports of laparoscopic adrenalectomy have included adrenal cancer. Mitotane as adjuvant therapy was found to be beneficial in a recent study with limitations being retrospective [102,103]. Detailed description of adrenal cortical carcinoma is beyond the scope of this chapter [104].

Follow-Up

Patients with nonfunctional tumors smaller than 4 cm in diameter should be followed up with serial CT scans at 6 months and 1 year [91], with a decrease in frequency thereafter (example at 2 and 4 years; incomplete evidence precludes very specific recommendations). Tumors that enlarge by more than 1 cm (5% of all tumors) during the follow-up period should be surgically removed. A recent retrospective study suggested an increase of 25% in size per year is indicative to detect malignancy. Periodical hormonal evaluation is supported by the fact that in approximately 0% to 24% of patients, new hormonal abnormalities may develop [105]. Long-term studies suggest that 5% to 20% tumors enlarge in size and 3% to 4% decrease in size. Recent meta-analysis showed actual rates of conversion to hormonal hyperfunction of only 1%, increase of size in 15%; authors question the serial follow-up when radiation exposure and cost of testing are taken into consideration [106].

ADRENAL INSUFFICIENCY

Definition

Adrenal insufficiency is characterized by deficiency of adrenal hormones. The etiology and the rate of onset of this condition determine the clinical presentation and laboratory findings. Primary adrenal insufficiency (PAI), also known as Addison disease, is due to dysfunction at the level of the adrenal glands and is typically associated with a low plasma cortisol level and an elevated plasma ACTH. Secondary adrenal insufficiency (SAI) is characterized by dysfunction at the level of the hypothalamus or pituitary gland that results in decreased ACTH production and the resulting decline in or lack of cortisol secretion [107].

Etiology and Epidemiology

The most common cause of adrenocortical failure is ACTH deficiency due to prolonged administration of exogenous glucocorticoid therapy (iatrogenic adrenal insufficiency). Various causes of PAI and SAI are listed in Table 3.4. Autoimmune adrenalitis accounts for most cases of PAI in industrialized nations. Antibodies against various steroidogenic enzymes, most frequently CYP21A2 (21-hydroxylase), are present in 65% to 85% of cases of primary autoimmune adrenal insufficiency [108]. Disseminated tuberculosis remains a significant cause of this condition in developing countries worldwide. A recent study from Sweden showed an increased risk of PAI in patients with celiac disease via the Swedish national register [109].

The term *relative adrenal insufficiency* has been extensively used in critical care literature. It includes "inadequate" production of corticosteroids during critical care illness, particularly sepsis. The endocrine criteria for definition of the condition vary and are unclear (nonstimulated cortisol during sepsis <20 μg/dl or an increment during cosyntropin stimulation <9 μg/dl). Initial studies with steroid treatment during septic shock were promising; a recently published CORTICUS trial showed that shock reversal occurred earlier with steroids, but there was no significant difference in 28-day mortality [110]. Interestingly, in a recent study, free cortisol levels were analyzed and survivors of septic shock had lower total and free cortisol levels than nonsurvivors and no difference between the groups was found [111]. Systematic review of 17 randomized trials showed 28-day mortality for treated versus controlled patients, 35.9% versus 38.5% (RR-0.84, CI 0.71–1.00), in a heterogenous study group population [112].

Pathophysiology

Secretion of cortisol is controlled primarily through the hypothalamus and pituitary gland, whereas aldosterone is predominantly regulated by the renin–angiotensin system. PAI is characterized by decreased production of both cortisol and aldosterone, with a compensatory increase in ACTH production, whereas SAI is associated with decreased levels of cortisol and ACTH, with preserved mineralocorticoid activity. In autoimmune adrenal insufficiency, the first evidence of a decline in adrenocortical function is an increase in PRA with a low or normal serum aldosterone concentration. This is followed by decreasing plasma cortisol response to ACTH stimulation, increased basal ACTH levels, and finally diminished basal plasma cortisol concentrations and symptoms.

Diagnosis

Clinical Symptoms

Clinical manifestations of adrenal insufficiency depend mainly on the acuteness and the degree of glucocorticoid and mineralocorticoid deficiency. Acute adrenal

Table 3.4. Etiologic Factors for Adrenal Insufficiency

Primary Adrenal Insufficiency
Autoimmune disease (common)
Isolated
Polyglandular autoimmune syndromes type I and II
Infectious etiologies
Disseminated tuberculosis (common)
Disseminated fungal infections
HIV infection
Other systemic bacterial infections
Inherited disorders
Adrenal leukodystrophy (rare)
Triple A syndrome
Kearns-Sayre syndrome
Hemorrhagic infarction
Sepsis (meningococcemia/*Pseudomonas aeruginosa*)
Anticoagulant therapy
Antiphospholipid antibody syndrome
Metastatic disease
Iatrogenic
Drugs: ketoconazole, aminoglutethimide, metyrapone, suramin, and etomidate
Infiltrative disorders
Congenital adrenal hyperplasia
Congenital adrenal hypoplasia (DAX-1-related forms)
Resistance to ACTH
Secondary and Tertiary Adrenal Insufficiency
Prolonged administration of exogenous corticosteroids (iatrogenic)
Isolated ACTH or CRH deficiency (rare)
Organic hypothalamic or pituitary gland disorders
Primary or metastatic tumors (including macroadenomas and craniopharyngiomas)
Infections
Hypophysitis
Granulomatous-type disorders
Sheehan syndrome
Parasellar lesions (meningiomas)
Prior radiation or neurosurgery
Peripheral resistance to glucocorticoids

insufficiency typically leads to shock, usually precipitated by a significant stress (surgery, infection). Decreased production of glucocorticoids and mineralocorticoids results in hypotension (diminished cardiac and peripheral vascular resistance), hypovolemia, hyponatremia, hyperkalemia, and metabolic acidosis. Weakness, fatigue, anorexia, nausea, abdominal pain, weight loss,

and orthostatic hypotension are common presenting features of a chronic form of this disease. Other manifestations include diarrhea, muscle aches, dizziness, and hypoglycemia. Hyperpigmentation can be seen in PAI, and it is caused by increase in pro-opiomelanocorticotrophic hormone, which leads to increase in melanin levels in skin.

Laboratory Diagnosis

Adrenocortical provocative tests are critical in the diagnosis of adrenal insufficiency (vide infra).

Plasma cortisol levels are usually at their peak in the early morning (between 4 and 8 a.m.) and further increase with stress; thus, a low plasma cortisol level (<3 μg/dl) provides presumptive evidence of adrenal insufficiency. Conversely, a high morning plasma cortisol concentration (>17 μg/dl) is highly predictive of a normal plasma cortisol response to insulin-induced hypoglycemia or ACTH administration [113]. However, patients with partial adrenal deficiency may demonstrate relatively normal morning levels, whereas low values can be seen in eucortisolemic patients (timing of sampling in regard to diurnal rhythm) and in patients with low cortisol-binding globulin. Likewise, although basal UFC and 17-hydroxycorticosteroid (17-OHCS) excretion are usually low in patients with severe adrenal insufficiency, patients with partial deficiencies may have low-normal values

ACTH (Cosyntropin) Stimulation Test

A normal response to high-dose (HST) ACTH (250-mg IV or IM bolus) stimulation test is an increase in plasma cortisol concentration after 30 to 60 minutes to a peak of at least 18 to 20 μg/dl (500–550 nmol/l). A normal response to high-dose ACTH stimulation excludes PAI [114] but not secondary disease. Prolonged SAI leads to adrenal atrophy, which will be seen as sluggish or inappropriate response to ACTH stimulation. However, in patients with mild or recent onset of SAI, ACTH stimulation test results will be normal and the only reliable tests are the insulin–hypoglycemia test or metyrapone test. The low-dose cosyntropin stimulation test (1 μg IV bolus) low-dose corticotropin test (LDT) with measurements of plasma cortisol at 15 and 30 minutes has been proposed to have slightly higher sensitivity than the standard stimulation tests in setting of SAI. Depending on the cutoff used in various studies (peak cortisol of 18–22 μg/dl), the sensitivity of the test varies between 65% and 100%, with specificity of 87% to 96% [115]. The need for meticulous dilution of the currently available cosyntropin vial makes the interpretation and reliability of the test more difficult. Note that recent meta-analysis of available studies showed both types of provocative tests to have similar sensitivities when specificities were set at 95% [116]. Additional meta-analysis reported that LDT was superior (AUC of 0.92 vs. HDT of 0.79) based on meta-analysis of 679 patients with secondary AI using a cortisol threshold of 16 μg/dl. This superiority needed exclusion of five studies with older fluorescence immunoassays and correction of plasma cortisol values to serum cortisol values [2]. Technical aspects influence the diagnostic accuracy of the LDT, particularly timing of the procedure and tubing used [117].

A subnormal response confirms the diagnosis of adrenal insufficiency, but further testing is needed to determine the cause of the condition. It is generally helpful to measure a baseline plasma ACTH before administration of cosyntropin. A recent analysis of salivary cortisol as an alternative for serum cortisol in LDT showed more dynamic responses for the salivary method, but sensitivity and specificity were too low to be alternatives [118].

Metyrapone Test
Refer to the section on evaluation of pituitary function.

Insulin Hypoglycemia Test
Refer to the section on evaluation of pituitary function.

Measurement of Adrenocorticotropic Hormone
Simultaneous measurement of ACTH and cortisol will differentiate primary from secondary causes of hypoadrenalism (plasma ACTH is elevated in PAI and low or low normal in secondary and tertiary disease).

Plasma Renin Activity and Aldosterone
The PRA and PRA-to-plasma or PRA-to-urinary-aldosterone ratio was elevated in 100% of the patients with PAI [114].

Corticotropin-Releasing Hormone Test
Secondary (pituitary) and tertiary (hypothalamus) adrenal insufficiency could be differentiated through the administration of CRH. ACTH and cortisol responses are minimal or absent with pituitary-related deficiency, whereas an exaggerated response is seen with hypothalamic disease. This is not now clinically useful.

Imaging Studies
In patients with PAI, CT of the abdomen with 3-mm cuts of adrenals is the preferred imaging study; when SAI is identified, MRI or CT of the sella turcica and hypothalamus with contrast is performed.

Treatment
The initial goals of therapy in a patient with acute adrenal insufficiency are volume resuscitation and correction of electrolyte abnormalities. Large amounts of 0.9% NaCl solution should be rapidly administered at about 2 to 3 l/h until the hypotension is corrected. Once the patient is fluid repleted, NaCl solution can be switched to 5% dextrose with 0.45% normal NaCl solution. Glucocorticoid deficiency should be addressed expeditiously by intravenous hydrocortisone (100-mg bolus) or dexamethasone (4-mg bolus). The latter can be used if further testing is required because it does not interfere with the measurement of cortisol. The 1st day, hydrocortisone, 100 mg every 6 to 8 hours, is continued and slowly tapered the next 3 to 4 days, depending on the level of stress. Maintenance dosing usually consists of 15 to 25 mg of hydrocortisone per day (lower doses supported more by recent new physiology data based on new assays) orally in two to three divided dosages, with the last dose not later than 5 to 6 p.m., or prednisone, 5 mg, in the morning. The requirement of two or three dosages of hydrocortisone is debatable, a recent study showing a more physiologic cortisol profile with three times daily dosing (10 mg–5 mg–5 mg), but a better health-related quality of life (HRQL) with a 20 mg–0 mg–10 mg regimen [119]. A questionnaire of 556 patients with primary or secondary AI showed a significantly impaired subjective health status compared with controls irrespective of prednisolone or hydrocortisone used for replacement [120]. Recently developed delayed- and extended-release hydrocortisone might represent future therapeutic options. Overreplacement with glucocorticoids is a frequently seen problem and should be avoided. In fact, Swedish patients with PAI were reported to have two times the mortality of age-matched controls [121]. Patients with PAI will require treatment with mineralocorticoid agents. Fludrocortisone is typically administered at a dose of 0.1 mg/d, but higher or lower dosage may be required, with adjustments based on symptoms, blood pressure, fluid retention, and serum sodium concentration. Transient glucocorticoid dose increases will be needed for stress or surgery.

Replacement of adrenal androgens is not yet a part of routine clinical practice. The results of several studies (performed only in women) show improvement in fatigue, well-being and sexuality [122], or insulin sensitivity [123] in some studies but not in others [124]. Dosages of 25 to 200 mg of DHES daily have been used, and hirsutism appears to be a major side effect. Treatment is further hampered by lack of pharmaceutically controlled preparations. Systematic review and meta-analysis of 10 eligible randomized controlled trials showed a small effect of HRQL and depression in women with adrenal insufficiency but no effect on anxiety and sexual well-being [125].

PHEOCHROMOCYTOMA

Steven A. De Jong

Definition and Etiology

Pheochromocytomas are catecholamine-producing neuroendocrine tumors that originate from chromaffin cells in the adrenal medulla or extra-adrenal paraganglia. Chromaffin cells develop from neuroectodermal tissue and are associated with the sympathetic ganglia. Although most such cells degenerate after birth, a large collection persists in the adrenal medulla. As a result, 90% of all pheochromocytomas are located in the adrenal medulla and 98% are located below the diaphragm in the posterior, central middle, or lower abdomen [126]. Extra-adrenal pheochromocytomas, also known as paragangliomas, are usually located along the sympathetic chain from the base of the skull to the bladder and are more frequently malignant. Paragangliomas derived from parasympathetic tissue often lack the ability to produce catecholamines. The most common extra-adrenal site for a pheochromocytoma is the organ of Zuckerkandl, a collection of paraganglion cells found near the origin of the inferior mesenteric artery and the bifurcation of the aorta [127]. Paragangliomas have been found adjacent to the thoracic or abdominal aorta, in the dome or trigone of the bladder, in the carotid body, and inside the heart. These extra-adrenal tumors are further characterized by an aberrant, unusually large blood supply. Pheochromocytomas are traditionally referred to as "the tumor of 10s" because 10% of these tumors are extra-adrenal, malignant, found in children, and bilateral, multiple, or familial. Recent data, however, suggest that 80% to 85% of pheochromocytomas arise from the adrenal medulla, 15% to 20% are of extra-adrenal origin, and 15% to 25% may be hereditary [128]. Familial pheochromocytomas are often multifocal or bilateral and generally present at an earlier age than the sporadic type. The cause is unknown, although chromosomal deletions and mutations have been identified in both sporadic and familial pheochromocytomas associated with the multiple endocrine neoplasia (MEN) type 2 syndromes, von Hippel-Lindau disease, neurofibromatosis type 1 disease, and familial pheochromocytoma/paraganglioma syndrome [126,127,129,130].

Epidemiology

A pheochromocytoma can occur at any age and has been described in both newborn and elderly patients. The peak incidence of these tumors occurs during the fourth and fifth decades of life, and they are uncommon after the age of 60 years. Both adrenal glands are affected equally, and no sexual predilection exists, aside from a slight increased female incidence in children. As one of the few rare curable causes of hypertension, pheochromocytomas are identified in only 0.1% to 0.6% of all hypertensive patients [131]. Autopsy studies show a relatively high prevalence of 0.3% to 0.95%, suggesting that a number of these tumors are missed and can result in premature mortality [132].

The current incidence of pheochromocytoma appears to be increasing, likely as the result of improved detection and screening. Biochemical screening results in a prevalence of 1.9%. Approximately one to two per 100,000 people harbor pheochromocytomas, and patients with unrecognized pheochromocytoma are at risk for significant morbidity and mortality [127,128]. Approximately 5% of incidentalomas are pheochromocytomas, and 25% of pheochromocytomas are discovered incidentally during unrelated imaging studies [131]. Complications manifested by hypertensive crisis alone or with shock leading to death may result from pharmacotherapy, anesthesia, childbirth, or surgery performed for other conditions.

Hereditary or familial pheochromocytomas are often bilateral and are frequent components of the inherited syndromes. Pheochromocytomas occur in 25% to 70% of patients with MEN type 2 syndrome, in 25% of patients with von Hippel-Lindau disease, and in fewer than 1% of patients with neurofibromatosis type 1 and von Recklinghausen disease [132]. Specific genetic testing identifying changes in the genetic mutations of the RET proto-oncogene have facilitated prompt accurate identification of patients with the MEN type 2 syndrome and timely treatment of associated pheochromocytoma and other endocrinopathies [133,130]. See the Chapter 9 on MEN.

Pathophysiology

Catecholamine synthesis begins in the cytoplasm of the chromaffin cells of the adrenal medulla. Phenylalanine and tyrosine undergo a series of hydroxylations and decarboxylations to form norepinephrine, which can be stored in and released from intracellular granules. Conversion from norepinephrine to epinephrine requires the enzyme phenylethanolamine-*N*-methyltransferase, which is found almost exclusively in the adrenal medulla and organ of Zuckerkandl. Epinephrine displays alpha (α) activity, manifested by vasoconstriction, and beta (β) activity that causes a lesser degree of vasodilation and tachycardia. Norepinephrine acts primarily by α-receptor stimulation, which results in profound vasoconstriction and reflex bradycardia. Epinephrine is four to six times more potent than norepinephrine and constitutes 85% of adrenal medullary catecholamine production. An epinephrine-producing pheochromocytoma is almost invariably localized to the adrenal medulla [127]. Conversely, extra-adrenal pheochromocytomas often lack the ability to produce epinephrine and thus secrete more norepinephrine. Significant variability is found in the amounts and types of catecholamines released by most pheochromocytomas, which explains the common pattern of paroxysmal symptoms. Pheochromocytomas also have the ability to produce and release other peptides such as calcitonin, vasoactive intestinal peptide, dopamine, neuropeptide Y, parathyroid-related hormone, and ACTH [126,129].

Most tumors that cause hypertension are 3 to 5 cm in diameter, but they can range in size from microscopic adrenal medullary hyperplasia to 30 cm in diameter. They can weigh between 1 g and 4 kg, with an average weight of 100 g [134]. Gross examination reveals a highly vascular gray to pinkish-tan tumor, and areas of hemorrhage, calcification, necrosis, and cystic degeneration are commonly seen. Microscopically, the tumors resemble the cell structure and appearance of the adrenal medulla. The histologic appearance of these tumors, even with capsular or vascular invasion, cannot reliably distinguish benign from malignant lesions. Malignancy is defined by tumor invasion outside the primary site of origin or the demonstration of metastatic disease to lymph nodes, liver, bone, lung, and, rarely, the central nervous system. Malignant pheochromocytomas tend to be larger with more necrosis and are slightly

more common in female patients. Malignancy is less common in pheochromocytomas associated with familial syndromes. DNA ploidy studies have been useful in the proper characterization of malignant tumors and may predict prognosis [135].

Diagnosis

The clinical presentation of pheochromocytoma is attributed to the physiology of excess circulating catecholamines; often a significant delay occurs between initial symptoms and final diagnosis [132]. The predominant sign is paroxysmal or sustained hypertension, although as many as 5% of patients with pheochromocytoma are normotensive. Patients with pheochromocytoma discovered incidentally are often normotensive. Other associated symptoms include palpitations, tachycardia, headache, diaphoresis, nausea, abdominal/chest pain, fever, flushing, vomiting, and anxiety or panic attacks [126,129]. Metabolic effects include hyperglycemia, lactic acidosis, and weight loss [136]. Biochemical screening should be performed in hypertensive children, pregnant patients, patients who are resistant to antihypertensive medication, young patients with new-onset hypertension, patients with hypertension associated with new or worsening diabetes, or patients with a hypertensive crisis after anesthesia, surgery, or medication administration. Family members of MEN type 2 syndrome patients should also be screened for pheochromocytoma, and most patients with pheochromocytoma should undergo genetic testing [137,138].

Measurement of plasma catecholamine and 24-hour urinary fractionated catecholamine, metanephrine, normetanephrine, and VMA production remain the cornerstone of the diagnosis of pheochromocytoma. Extra-adrenal paragangliomas are common in patients with predominant elevation of urinary norepinephrine. Plasma free catecholamine (metanephrine and normetanephrine) levels have also played an increasingly significant role in detecting pheochromocytoma [139]. In one of the largest studies on biochemical diagnosis of pheochromocytoma, the sensitivity of plasma free metanephrines was found to be 99%, and specificity was 89%, compared with urinary catecholamines of 86% and 88%, respectively. Because of a high negative predictive value, many argue that a normal plasma metanephrine level is sufficient to exclude the diagnosis of pheochromocytoma [130]. Plasma catecholamine sensitivity was 84%, with a specificity of 81% [140]. False-positive results often exceed true-positive results, as many physiologic stimuli, drugs, dietary interferences, or any clinical condition that increases circulating catecholamines can produce false-positive testing. Discontinuation or substitution of medications such as tricyclic antidepressants and amphetamines can improve the accuracy of urinary and plasma testing for pheochromocytoma [141]. Plasma and urinary catecholamines that are elevated two to four times above the normal values confirm the presence of pheochromocytoma, and provocative testing, by using glucagon, histamine, and other agents, is now unnecessary and is associated with considerable morbidity and mortality. Suppression testing by using clonidine is rarely needed and may cause unexpected hypotension in patients with pheochromocytoma medicated with α-adrenergic and β-blocking agents [142]. This centrally acting α_2 agonist is unable to suppress the secretion of epinephrine and norepinephrine in pheochromocytoma and has a reported historical accuracy rate of 92% [143]. Finally, serum chromogranin A levels were found to be elevated in 86% of patients with pheochromocytoma, but lower sensitivity and specificity rates have limited its usefulness in diagnosis [119]. These levels, however, can be useful in the surveillance of malignant pheochromocytoma as a marker of tumor burden and progression of disease [130].

Treatment

Medical blockade of excess catecholamine production should be started as soon as the diagnosis of pheochromocytoma is confirmed. Phenoxybenzamine, a long-acting noncompetitive presynaptic and postsynaptic α-adrenergic antagonist, is started 1 to 3 weeks before surgical resection at 20 mg/d in divided doses and gradually increased every few days until blood pressure normalizes and the patient experiences mild postural hypotension and nasal congestion. The daily dose can be as high as 1 mg/kg, with the goal of blood pressure control, symptom relief, and volume replacement before surgical intervention. Other agents useful for refractory patients include prazosin, doxazosin, terazosin, calcium channel blockers, phentolamine, and metyrosine [141]. Labetolol has both α- and β-receptor antagonistic activity and has been successfully used for preparation, but patient response may be variable [130,145]. Isolated β-blocker therapy, usually in the form of propranolol in doses of 10 to 40 mg every 6 to 8 hours, may be required for patients with tachycardia or cardiac arrhythmias [129,134] that persist or develop during medical preparation. Hypertensive crisis, cardiac arrhythmias, acute cardiac failure/ischemia, pulmonary edema, and cerebral vascular accident can occur if β-blockers are started before complete α-blockade and volume restoration is achieved. Metyrosine can also decrease serum catecholamine levels through inhibition of tyrosine kinase, the rate-limiting enzyme involved in catecholamine synthesis. Intraoperative control of blood pressure can be achieved with intravenous phentolamine, sodium nitroprusside, nitroglycerine, magnesium sulfate, and urapidil, while cardiac tachyarrhythmias are best managed with short-acting β-blockers such as esmolol or labetalol [146].

Surgical resection after adequate localization and medical preparation remains the definitive treatment for all patients with sporadic or familial pheochromocytoma or paraganglioma. Given that 98% of all pheochromocytomas are found in the abdomen, preoperative tumor localization is safely and successfully accomplished with MRI scanning of the adrenal glands, abdomen, and pelvis [147]. CT scanning of the adrenal glands and entire abdomen with and without contrast is another suitable imaging option for patients whose excess catecholamine production has been medically controlled. Pheochromocytomas typically appear as a dense, vascular mass with slow washout of administered intravenous contrast. It is important to visualize a normal contralateral adrenal gland because 10% to 20% of pheochromocytomas are bilateral; familial disease is commonly bilateral although clinically asynchronous. Occasionally, iodine-131-labeled metaiodobenzylguanidine (^{131}I-MIBG) or preferably ^{123}I-MIBG is needed to identify extra-adrenal tumors in patients with negative CT or MRI imaging or in patients with malignant pheochromocytoma to detect distant sites of tumor metastasis. This imaging modality is also useful in malignant pheochromocytoma for diagnosis and staging as it may detect tumor metastasis too small to be seen on CT or MRI. Finally, evidence suggests that 6-^{18}F-fluorodopamine PET scanning, although not uniformly available or advisable as the initial localization study, may be more sensitive than MIBG for visualization of pheochromocytoma. Twenty-nine patients with pheochromocytoma were evaluated with MIBG and PET scans using 2-fluoro-2-deoxy-D-glucose (FDG) [41]. Four patients were found to have positive PET scans and negative levels of MIBG. Of those patients with positive PET and MIBG scans, the PET scans were superior to MIBG in 56% and determined to be as good as or better than MIBG in 88% of cases. Failure to localize the pheochromocytoma with CT, MRI, or radionuclide scanning should suggest careful reevaluation of the diagnosis.

The principles of safe extirpation include careful and complete intraoperative monitoring, stress-free anesthesia, complete tumor resection, minimal tumor manipulation, avoidance of tumor seeding, meticulous hemostasis, and early control of the vascular supply and venous drainage of the tumor. Many such tumors can be removed by using a laparoscopic approach in experienced centers to reduce postoperative morbidity and pain, to shorten hospital stay, and to decrease expense compared with traditional laparotomy [144]. The complication rate is less than 8%, operative mortality is 1% to 2%, and the open conversion rate is 5% [148]. Tumors larger than 7 cm in diameter may be malignant and often should be removed with an anterior or thoracoabdominal approach. Laparoscopic bilateral adrenal resection can also be performed if indicated as a single or staged procedure with or without adrenocortical-sparing techniques. Postoperative hypotension and hypoglycemia may develop and may require transient intravenous inotropic and glucose administration, and the overall rate of recurrence is 0% to 17% [149].

Malignant pheochromocytomas are often treated with initial or reoperative radical surgical removal to improve symptoms, decrease tumor burden, and improve survival, with variable results. Hepatic resection or ablation can be considered for localized metastases, whereas arterial embolization, radiofrequency ablation (RFA), chemoembolization, and cryoablation can be useful for diffuse hepatic disease [150,151]. Medical control of symptoms is achieved with α-adrenergic blockers, and treatment with chemotherapeutic agents has resulted in disappointing results [141]. Radioactive ablation with high-dose ^{131}I-MIBG has been moderately successful to prolong survival and provide effective palliation in some patients, but further studies are needed to confirm benefit [152,153].

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Evaluation of Adrenocortical Function

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   (Adrenal Insufficiency) Meta-analysis patient-level data from 13 studies (n = 679) evaluating diagnostic value of standard-dose (HDT) or low-dose corticotropin tests (LDT) performed in patients with suspicion of hypothalamic–pituitary–adrenal insufficiency (HPAI), with exclusion of studies where no insulin hypoglycemia or metyrapone test was not standard for HPAI, if subjects were in intensive care unit, or if only healthy controls were used. Calculated area under receiver-operating characteristic (ROC) curve was for LDT 0.92 (95% CI = 0.89–0.94), for

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    This extensive review provides detailed information on all aspects of the disease.

49. (3) **Schwartz GL, Turner ST.** Prevalence of unrecognized primary aldosteronism in essential hypertension [abstract]. Am J Hypertens 2002;15:18A.

    This abstract describes a change in the prevalence of primary hyperaldosteronism in patients presumed to have essential hypertension.

50. (2) **Young WF Jr,** et al. Primary hyperaldosteronism: Diagnosis and treatment. Mayo Clin Proc 1990;65:96–110.

    This reference is a practical guide to the clinical presentation and treatment of this disorder.

51. (2) **Li JT,** et al. Aldosterone-secreting adrenal cortical adenocarcinoma in an 11-year-old child and collective review of the literature. Eur J Pediatr 1994;153:715–717.

    This case report describes the aspects of primary hyperaldosteronism seen in patients with adrenocortical carcinoma and review of the current literature on this subject.

52. (3) **McKenzie TJ,** et al. Aldosteronomas—state of the art. Surg Clin N Am 2009;89:1241–1253.

    This review article summarizes the diagnosis, imaging, and treatment of aldosteronoma. Emphasis is placed on an increase in the prevalence of the disorder, changing patterns of clinical presentation, and the various tools available to distinguish primary from secondary hyperaldosteronism. Strategies are described to differentiate unilateral from bilateral disease, and surgical treatment options are discussed.

53. (1) **Rossi E,** et al. High prevalence of primary aldosteronism using postcaptopril plasma aldosterone to renin ratio as a screening test among Italian hypertensives. Am J Hypertens 2002;15(10 pt 1):896–902.

    This study assessed the prevalence of primary hyperaldosteronism, use of captopril stimulation for screening, and the rising incidence of normokalemia in this adrenal disorder.

54. (2) **Young WF Jr.** Minireview: primary aldosteronism—changing concepts in diagnosis and treatment. Endocrinology 2003;144(6):2208–2213.

This reference reviews the increased incidence of primary hyperaldosteronism in hypertensive patients and the required screening studies needed to confirm the diagnosis. Surgical treatment is advisable for unilateral disease while bilateral hyperplasia is treated with medical therapy.

55. (1) **Weinberger MH, Fineberg NS.** The diagnosis of primary hyperaldosteronism and separation of two major subtypes. Arch Intern Med 1993;153:2125–2129.

    This publication describes techniques helpful in determining the etiology of hyperaldosteronism. It concludes that the use of the plasma aldosterone/PRA ratio appears to be useful in the screening, diagnosis, and differentiation of unilateral and bilateral forms of primary hyperaldosteronism. These observations may also be applicable to patients receiving some antihypertensive medications.

56. (1) **Nomura K,** et al. Plasma aldosterone response to upright posture and angiotensin II infusion in aldosterone-producing adenoma. J Clin Endocrinol Metab 1992;75(1):323–326.

    This study of 19 patients with primary aldosteronism, due to surgically confirmed APA, evaluated the response of aldosterone to upright posture and angiotensin II infusion in distinguishing between APA and idiopathic hyperaldosteronism.

57. (1) **Kem DC,** et al. The prediction of anatomical morphology of primary aldosteronism using serum 18-hydroxycorticosterone. J Clin Endocrinol Metab 1985;60(1):67–73.

    This study examines the role of measuring serum 18-hydroxycorticosterone, aldosterone, and potassium under basal conditions in 34 patients with documented primary aldosteronism. Determination of serum 18-hydroxycorticosterone is a useful predictor of the etiology of primary aldosteronism.

58. (2) **Young WF,** et al. Role for adrenal venous sampling in primary aldosteronomas. Surgery 2004;136:1227–1235.

    This study provides detailed information on a large patient population undergoing adrenal vein sampling for primary hyperaldosteronism. Many technical aspects of the procedure and clinical features of the disease are discussed.

59. (1) **Doppman JL,** et al. Distinction between hyperaldosteronism due to bilateral hyperplasia and unilateral aldosteronoma: Reliability of CT. Radiology 1992;184:677–682.

    This study compared the efficacy of CT and adrenal vein sampling in 24 patients with primary hyperaldosteronism. CT diagnosed unilateral adenoma in 19 patients and hyperplasia in 7 patients. After AVS, unilateral adenoma was diagnosed in 22 patients. In their study, six of seven patients with bilateral nodules were found to have unilateral adenoma after venous sampling.

60. (1) **Young WF Jr,** et al. Role for adrenal venous sampling in primary aldosteronism. Surgery 2004;136(12):1227–1235.

    This prospective study of 203 patients with primary hyperaldosteronism confirms the hypothesis that adrenal vein sampling is an essential diagnostic step in most patients to distinguish between unilateral and bilateral adrenal aldosterone hypersecretion.

61. (1) **Nocaudie-Calzada M,** et al. Efficacy of iodine-131 6-beta-methyl-iodo-19-norcholesterol scintigraphy and computed tomography in patients with primary aldosteronism. Eur J Nucl Med 1999;26:1326–1332.

    This article reports on 41 patients who underwent CT and adrenal scintigraphy. Correct diagnosis was made in 92% of cases compared with only 58% by using CT alone.

62. (2) **Weigel RJ,** et al. Surgical treatment of primary hyperaldosteronism. Ann Surg 1994;219:347–352.

    This article summarizes the surgical care of a patient with an aldosteronoma and describes long-term results of resection.

63. (1) **Rossi GP,** et al. Identification of the etiology of primary aldosteronism with adrenal vein sampling in patients with equivocal computed tomography and magnetic resonance findings: results in 104 consecutive cases. J Clin Endocrinol Metab 2001;86(3):1083–1090.

    This study of 104 patients investigates the usefulness of adrenal vein sampling in identifying the etiology of primary aldosteronism in patients with equivocal CT and MR findings.

64. (1) **Celen O,** et al. Factors influencing outcome of surgery for primary hyperaldosteronism. Arch Surg 1996;131:646–650.

    This article summarizes the role and predictive factors of successful surgery for primary hyperaldosteronism. The study of 42 patients who underwent adrenalectomy for primary hyperaldosteronism between the years 1970 and 1993 showed that the main determinants

of a surgical cure of hypertension in primary hyperaldosteronism were presence of adenoma and preoperative response to spironolactone. The authors favored CT as the initial modality to establish preoperative diagnosis of adenoma because of its reproducibility and high specificity.

65. (1) **Krum H,** et al. Efficacy of eplerenone added to renin-angiotensin blockade in hypertensive patients. Hypertension 2002;40(2):117–123.

This study of 341 hypertensive patients examines the efficacy and tolerability of eplerenone, a selective aldosterone blocker, when added to existing antihypertensive therapy with an ACE inhibitor or an angiotensin II receptor blocker.

Cushing Syndrome

66. (3) **Catargi B,** et al. Occult Cushing's syndrome in type-2 diabetes. J Clin Endocrinol Metab 2003;88:5808–5813.

Cross-sectional study of 200 overweight patients with type 2 DM with poor diabetic control. Definitive CS was identified in 2% patients. Fifty-two patients had impaired 1-mg DST requiring further testing.

67. (3) **Chiodini I,** et al. Subclinical hypercortisolism among outpatients referred for osteoporosis. Ann Intern Med 2007;147:541–548.

Two-hundred patients without clinically overt hypercortisolism or other secondary causes of osteoporosis in a tertiary referral center had a prevalence of CS of 4.8%; the prevalence of CS was 10.8% in patients with vertebral fractures.

68. (3) **Mullan K,** et al. Is there value in routine screening for Cushing's syndrome in patients with diabetes? J Clin Endocrinol Metab 2010;95:2262–2265.

Consecutive patients (n = 200) with diabetes and 79 controls were studied, and no diagnosis of CS was made, although substantial proportion of patients had false-positive LNSC.

69. (3) **Raff H,** et al. A physiologic approach to diagnosis of the Cushing syndrome. Ann Intern Med 2003;138:980–991.

This article provides an excellent overview of CS.

70. (3) **Ilias I,** et al. Cushing's syndrome due to ectopic corticotropin secretion: twenty years' experience at the National Institutes of Health. J Clin Endocrinol Metab 2005;90:4955–4962.

Retrospective analysis of extensive tertiary care experience with 86 patients with ectopic CS. IPSS was the best test to identify the diagnosis; initial localization failure is common and suggests pulmonary carcinoid. Forty-seven percent of patients achieved cure.

71. (4) **Lacroix A,** et al. Bilateral adrenal Cushing's syndrome: Macronodular adrenal hyperplasia and primary pigmented nodular adrenocortical disease. Endocr Metab Clin North Am 2005;34:441–458.

Detailed review of in vitro and in vivo evidence of ectopic abnormal adrenal membrane receptors causing ACTH-independent CS. Strategies for the investigation, as well as opportunities of new pharmacologic therapies, are discussed.

72. (4) **Pivonello R,** et al. The metabolic syndrome and cardiovascular risk in Cushing's syndrome. Endocr Metab Clin North Am 2005;34:327–339.

In-depth review of metabolic syndrome in setting of CS, including changes after remission of the disease

73. (2) **Van Zaane B,** et al. Hypercoagulable state in Cushing's syndrome: a systematic review. J Clin Endocrinol Metab 2009;94:2743–2750.

Meta-analysis of 15 reports on coagulation and fibrinolysis of various types of studies, no high-quality studies identified. A risk of 1.9% and 2.5% was reported for venous thromboembolism (VTE) not provoked by surgery, whereas postoperative risk of VTE was 0% to 5.6%.

74. (2) **Lindsay JR,** et al. Long-term impaired quality of life in Cushing's syndrome despite initial improvement after surgical remission. J Clin Endocrinol Metab 2006;91:447–453.

CS (studied prospectively in 23 patients) was associated with impaired HRQL, which partially resolved after treatment. Additionally, authors studied 343 CS patients in remission up to 26 years after surgery. At longer-term follow-up of the large cross-sectional group, there was also residual impairment of HRQL. The data was calculated as z-scores for short-form 36 domains, and scores were compared with age- and sex-matched controls.

75. (2) **Putignano P,** et al. Midnight salivary cortisol versus urinary free and midnight serum cortisol as screening tests for Cushing's syndrome. J Clin Endocrinol Metab 2003;88:4153–4157.

Authors compare diagnostic performance of UFC with that of midnight serum cortisol and midnight salivary cortisol in differentiating 41 patients with CS from 33 with pseudo-CS, 199 with simple obesity, and 27 healthy normal-weight volunteers. Overall diagnostic accuracy for UFC was 95.3%, sensitivity 90.2%, specificity 96% (using a cutoff of ≥120 μg/24 hr), and similar to the two other screening tests.

76. (3) **Invitti C,** et al. Diagnosis and management of Cushing's syndrome: Results of an Italian multicenter study: Study Group of the Italian Society of Endocrinology on Pathophysiology of the Hypothalamic-Pituitary-Adrenal Axis. J Clin Endocrinol Metab 1999;84:440–448.

    This retrospective analysis of 426 patients with CS (288 with Cushing disease, 80 with adrenal adenoma, 24 with adrenal carcinoma, 25 with ectopic CRH, and nine with ACTH-independent nodular adrenal hyperplasia) showed that overnight low-dose suppression test that is considered as a screening test for CS was as reliable (95% accuracy) as the standard 2-day low-dose DST.

77. (3) **Findling J,** et al. The low-dose dexamethasone suppression test: A reevaluation in patients with Cushing's syndrome. J Clin Endocrinol Metab 2004;89:1222–1226.

    Authors assess diagnostic utility of overnight 1-mg DST and the 2-day, low-dose DST in 103 patients with CS. Fourteen patients suppressed serum cortisol to less than 5 μg/dl, whereas six patients actually suppressed it to less than 2 μg/dl after a 1-mg test. In addition, the 2-day, low-dose DST yielded false-negative results in 38% of patients when urine cortisol was used.

78. (4) **Liu H,** et al. Update on the diagnosis of Cushing syndrome. Endocrinologist 2005;15:165–180.

    Detailed, practical description and literature analysis of definitive diagnosis, as well as special challenges in diagnosis and differential diagnosis of CS.

79. (2) **Yanowski JA,** et al. Corticotropin-releasing hormone stimulation following low-dose dexamethasone administration: A new test to distinguish Cushing's syndrome from pseudo-Cushing's states. JAMA 1993;269:2232–2238.

    Fifty-eight adults with mild hypercortisolism (24-hour urine free cortisol level, 1,000 nmol/d; surgically confirmed CS in 39 patients, pseudo-Cushing in 19) were given 0.5 mg dexamethasone orally every 6 hours for 2 days, followed 2 hours later by ovine CRH (1-μg/kg intravenous bolus). Using 24-hour UFC criterion for CS diagnosis on the 2nd day of dexamethasone administration of greater than 100 nmol/d, the test had 100% specificity, 56% sensitivity, and 71% diagnostic accuracy. A plasma cortisol concentration above 1.4 μg/dl measured 15 minutes after CRH administration correctly identified all cases of CS and all cases of pseudo-Cushing states (100% specificity, sensitivity, and diagnostic accuracy).

80. (3) **Erickson D,** et al. Dexamethasone-suppressed corticotropin-releasing hormone stimulation test for diagnosis of mild hypercortisolism. J Clin Endocrinol Metab 2007;92:2972–2976.

    Retrospective analysis of dexamethasone-suppressed CRH stimulation test in 21 patients with mild CS versus 30 patients with pseudo-CS. The highest sensitivity of 90% and specificity of 90% were provided with a post-CRH cortisol at 15 minutes greater than 2.5 μg/dl, and with serum ACTH level at 15 minutes post-CRH greater than 27 pg/ml; sensitivity 95%, specificity 97%.

81. (3) **Valassi E,** et al. Concomitant medication use can confound interpretation of the combined dexamethasone-corticotropin releasing hormone test in Cushing's syndrome. J Clin Endocrinol Metab 2009;94:4851–4859.

    The specificity of the test was significantly influenced by use of extensive list of medications, which are provided in the article ($p = 0.014$).

82. (3) **Avgerinos P,** et al. The metyrapone and dexamethasone suppression tests for the differential diagnosis of the ACTH-depended Cushing's syndrome: A comparison. Ann Intern Med 1994;121:318–327.

    Retrospective cohort of 186 patients with ACTH-dependent CS. Criteria of more than 90% urinary cortisol suppression after 2-day HDDS test had sensitivity of 59%, specificity of 73%, and diagnostic accuracy of 61% for diagnosis of pituitary-dependent Cushing disease. Similar values (54%, 73%, and 58%, respectively) were achieved when criteria of more than 69% 24-hour urinary suppression of 17-hydroxysteroids was applied.

83. (3) **Dichek HL,** et al. A comparison of the standard high dose dexamethasone suppression test and the overnight 8 mg dexamethasone supression test for the differential diagnosis of adrenocorticotropin dependent Cushing's syndrome. J Clin Endocrinol Metab 1994;78:418–422.

A direct comparison of the standard HDDS test and the overnight DSTs performed in 41 patients (34 with Cushing disease and 7 with ectopic ACTH syndrome). The sensitivity of the tests was comparable: 79% versus 71% with a specificity of 100%; however, a postdexamethasone cortisol decline of more than 68% for the latter was used. The diagnostic performance of combining both tests was better than either test alone.

84. (3) **Aron DE,** et al. Effectiveness versus efficacy: The limited value in clinical practice of high-dose dexamethasone suppression test in differential diagnosis of ACTH dependent Cushing's syndrome. J Clin Endocrinol Metab 1997;82:1780–1785.

The sensitivity and specificity of HDDS for the diagnosis of pituitary-dependent CS are reported to be 81% and 66.7%, respectively, based on standard criteria of more than 50% suppression of baseline plasma or 24-hour urinary cortisol.

85. (2) **Assalia A,** et al. Laparoscopic adrenalectomy. Br J Surg 2004;91:1259–1274.

Meta-analysis of 20 comparative case-control studies comparing laparoscopic adrenalectomy with open adrenalectomy (2,550 procedures, including 225 patients with CS). The results of laparoscopic adrenalectomy were reproducible, associated with lower morbidity (10.9% vs. 35%), less blood loss (154 vs. 309 ml), similar hormonal outcome, and shorter hospital stay (12 vs. 18.2 days).

86. (2) **Engelhardt D,** et al. Therapy of Cushing's syndrome with steroid biosynthesis inhibitors. J Steroid Biochem Mol Biol 1994;49:261–267.

Meta-analysis of 82 patients with Cushing disease treated with ketoconazole. Daily doses of 400 to 1,600 mg effectively reduce plasma cortisol in 70% of patients. Long-term follow-up data were not included. Results in 26 patients with CS are presented as well.

87. (3) **Luton JP,** et al. Treatment of Cushing's disease by O,p'DDD: Survey of 62 cases. N Engl J Med 1979;300:459–464.

Retrospective review of cases treated with up to 12 g of mitotane daily, which achieved remission in 83% of patients. One-third continued to be in remission after therapy discontinuation.

88. (4) **Schteingart DE.** Drugs in the medical treatment of Cushing's syndrome. Expert Opin Emerg Drugs 2009;14:661–671.

Concise review of available medications for medical therapy of Cushing disease with review potential new avenues of exploration

89. (2) **Boscaro M,** et al. Treatment of pituitary-dependent Cushing's disease with the multireceptor ligand somatostatin analog pasireotide (SOM230): a multicenter, phase II trial. J Clin Endocrinol Metab 2009;94:115–122.

Phase II, open-label, single-arm, multicenter study in 39 patients with CS. Patients received pasireotide 600 μg twice a day for 15 days. Normalization of UFC occurred in five (17%) patients, and 76% showed a reduction in UFC.

Adrenal Incidentalomas

90. (3) **Herrera MF,** et al. Incidentally discovered adrenal tumors: An institutional perspective. Surgery 1991;110:1014–1021.

Some 2,066 patients with adrenal masses were analyzed from a total of 61,054 CT scans done from 1985 through 1989. Excluding patients with previous or concurrent malignancies, adrenal tumors localized after biochemical documentation of disease, and adrenal nodules smaller than 1 cm, 342 patients were analyzed, including 136 men and 206 women with a mean age of 62 years. Tumor diameter ranged from 1 to 11 cm (mean, 2.5 cm). Histologic diagnosis was available in 55 patients at the time of adrenalectomy; malignancy was discovered in five patients (four primary and one metastatic); the smallest malignant tumor detected measured 5 cm.

91. (4) **Grumbach M,** et al. Management of clinically inapparent adrenal mass ("incidentaloma"): NIH conference. Ann Intern Med 2003;138:424–429.

The NIH Consensus Development Program convention of experts in field report to address prevalence, causes, evaluation, and treatment of adrenal masses. Panel recommendation included 1-mg DSTs and measurement of plasma free metanephrines for patients with adrenal incidentalomas, serum potassium, plasma aldosterone/renin values in hypertension.

92. (3) **Mantero F,** et al. A survey on adrenal incidentaloma in Italy: Study Group on Adrenal Tumors of the Italian Society of Endocrinology. J Clin Endocrinol Metab 2000;85:637–644.

This was a multicenter retrospective study of 1,096 incidentalomas from 1980 to 1995. Questionnaires were obtained from 1,004 patients (420 men and 584 women), with a median age of 58 years. Mass size ranged from 0.5 to 25 cm (median, 3.0 cm). Some 85% of the masses

were nonfunctional; 9.2% were defined as representing SCS; 4.2% were pheochromocytomas; and 1.6% were aldosteronomas. Patients with SCS showed low baseline ACTH in 79%, cortisol unsuppressibility after 1 mg dexamethasone in 73%, above-normal UFC in 75%, disturbed cortisol rhythm in 43%, and blunted ACTH response to CRH in 55%. Adrenalectomy was performed in 380 patients; 198 cortical adenomas (52%), 47 cortical carcinomas (12%), 42 pheochromocytomas (11%), and other less-frequent tumor types were found. Patients with carcinoma were significantly younger (median, 46 years; range, 17–84 years) than patients with adenoma (median, 57 years, range, 16–83 years; $p = 0.05$), and adenomas were significantly smaller than carcinomas (3.5, 1–15 vs. 7.5, 2.6–25 cm; $p < 0.001$). A cutoff of 4 cm had the highest sensitivity (93%) in differentiating between benign and malignant tumors. Only 43% of patients with pheochromocytomas were hypertensive, and 86% showed elevated urinary catecholamines. All patients with aldosteronomas were hypertensive and had suppressed upright PRA.

93. (2) **Lenders J,** et al. Biochemical diagnosis of pheochromocytoma: Which is the best test? JAMA 2002;287:1427–1434.

    Multicenter cohort study of 214 patients with pheochromocytomas (large proportion with hereditary disease) and 644 patients without pheochromocytomas. Sensitivities and specificities of various tests were as follows: 99% and 89% for plasma free metanephrines, 97% and 69% for urinary fractionated metanephrines, 84% and 81% for plasma catecholamines, 77% and 93% for urinary total metanephrines, and 64% and 95% for urinary VMA, respectively.

94. (3) **Sawka AM,** et al. A comparison of biochemical tests for pheochromocytoma: measurement of fractionated plasma metanephrines compared with the combination of 24-hour urinary metanephrines and catecholamines. J Clin Endocrinol Metab 2003;88:553–558.

    Retrospective analysis of 31 patients with catecholamine-secreting tumors and 261 patients without pheochromocytoma. The sensitivity of fractionated plasma metanephrines and 24-hour urinary total metanephrines and catecholamines (either test positive) were 97% and 90%, respectively; however, the specificity for these were 85% and 98%, respectively. Authors' recommendation is that plasma metanephrine collection is the test of choice in high-risk patients (adrenal vascular mass, familiar syndromes).

95. (4) **Terzolo M,** et al. Subclinical Cushing's syndrome in adrenal incidentalomas. Endocrinol Metab Clin North Am 2005;34:423–439.

    Excellent up-to-date review of the topic

96. (2) **Masserini B,** et al. The limited role of midnight salivary cortisol levels in the diagnosis of subclinical hypercortisolism in patients with adrenal incidentaloma. Eur J Endocrinol 2009;160:87–92.

    Sensitivity of LNSC was only 22% among a prospectively studied group of 103 patients with adrenal incidentalomas of whom 22 patients were diagnosed with SCS.

97. (2) **Tauchmanova L,** et al. Patients with subclinical Cushing's syndrome due to adrenal adenoma have increased cardiovascular risk. J Clin Endocr Metab 2002;87:4872–4878.

    Cross-sectional study of 28 consecutive SCS patients compared with 100 matched controls. Systolic and diastolic pressure, fasting glues, insulin, total cholesterol, triglycerides, fibrinogen, and mean carotid artery intima–media thickness were higher in patients. Of the patients, 60.7% had hypertension, 71% had lipid abnormalities, 29% had impaired glucose tolerance, and 54% had impairment in hemostatic parameters. Eight patients underwent surgical removal of the adenoma, and on median follow-up of 44 months, a significant decrease of body mass index, systolic and diastolic blood pressures, and fibrinogen levels occurred ($p < 0.005$).

98. (3) **Chiodini I,** et al. Bone mineral density, prevalence of vertebral fractures, and bone quality in patients with adrenal incidentalomas with and without subclinical hypercortisolism: an Italian multicenter study. J Clin Endocrinol Metab 2009;94:3207–3214.

    Retrospective multicenter study of 287 patients with adrenal incidentaloma (with or without SCS) and 194 controls. Bone mineral density was significantly lower in SCS patients than other two groups, and patients with SCS had higher fracture prevalence (70.6%, 22%, 21.8%, $p < 0.0001$), regardless of age, BMD, menopause, and gender.

99. (3) **Hamrahian AH,** et al. Clinical utility of noncontrast computed tomography attenuation value (hounsfield units) to differentiate adrenal adenomas/hyperplasias from nonadenomas: Cleveland Clinic experience. J Clin Endocrinol Metab 2005;90:871–877.

    Retrospective review of the value of CT imaging attenuation value (HU) in 299 cases of adrenalectomies. The sensitivity and specificity for 10- and 20-HU cutoff values to differentiate adenoma/hyperplasia from nonadenomas were 40.5% and 100% and 58.2% and 96.9%, respectively.

100. (2) **Toniato A,** et al. Surgical versus conservative management for subclinical Cushing syndrome in adrenal incidentalomas: a prospective randomized study. Ann Surg 2009;249:388–391.

Prospective, randomized study (over 15 years) of 45 patients with SCS who were randomized to surgery or conservative management. In the first group, DM improved or normalized in 62.5% cases, hypertension improved in 67%, hyperlipidemia in 37.5%, obesity in 50% cases. Some worsening of DM, hypertension, hyperlipidemia was noted in the later group.

101. (2) **Assalia A, Gagner M.** Laparoscopic adrenalectomy. Br J Surg 2004;91:1259–1274.

Meta-analysis of 20 comparative case-control studies comparing laparoscopic adrenalectomy with open adrenalectomy (2,550 procedures, including 225 patients with CS). The results of laparoscopic adrenalectomy were reproducible, associated with lower morbidity (10.9% vs. 35%), less blood loss (154 vs. 309 ml), similar hormonal outcome, and shorter hospital stay (12 vs. 18.2 days).

102. (3) **Icard P,** et al. Adrenocortical carcinomas: Surgical trends and results of a 253-patient series from the French association of Endocrine Surgeons study group. World J Surg 2001;25:891–897.

Results of a large cohort of patients with adrenal cortical cancer are presented. Adjuvant mitotane after complete resection has not shown to provide survival benefit.

103. (2) **Terzolo M,** et al. Adjuvant mitotane treatment for adrenocortical carcinoma. N Engl J Med 2007;356:2372–2380.

Retrospective multicenter analysis of 177 patients with adrenocortical cancer who after radical surgery received adjuvant mitotane versus not (two control groups). Recurrence-free survival was prolonged in the mitotane group: 42 versus 10 or 25 months in two control groups.

104. (4) **Phan AT**. Adrenal cortical carcinoma—review of current knowledge and treatment practices. Hematol Oncol Clin North Am 2007;21:489–507; viii–ix.

Excellent, in-depth review of the topic of adrenal carcinoma

105. (2) **Vassilatou E,** et al. Hormonal activity of adrenal incidentalomas: results from a long-term follow-up study. Clin Endocrinol (Oxf) 2009;70:674–679.

Prospective, long-term follow-up of 77 patients with adrenal incidentalomas (mean 67 months). During follow-up, SCS was diagnosed in 12 patients out of 57 with normal function at baseline. A change in size of mass greater than 0.5 cm was observed in 26 patients.

106. (2) **Cawood TJ,** et al. Recommended evaluation of adrenal incidentalomas is costly, has high false-positive rates and confers a risk of fatal cancer that is similar to the risk of the adrenal lesion becoming malignant; time for a rethink? Eur J Endocrinol 2009; 161:513–527.

Meta-analysis of 20 papers with incidentally detected adrenal masses and follow-up. The development of functionality less than 1% or malignancy 0.2% was felt to be low as compared to false-positive rates of recommended investigations that typically 50 times greater than true-positive rates. The dose of radiation with each additional CT imaging and risk of cancer due to imaging-associated radiation exposure needs to be taken into consideration.

Adrenal Insufficiency

107. (4) **Arlt W,** et al. Adrenal insufficiency. Lancet 2003;361:1881–1893.

This is an excellent review of the etiology, pathogenesis, clinical presentation, and diagnostic workup of adrenal insufficiency. Therapy for adrenal insufficiency is discussed in detail as well.

108. (3) **Falorni A,** et al. Italian Addison Network study: Update on diagnostic criteria for the etiological classification of primary adrenal insufficiency (PAI). J Clin Endocrinol Metab 2004;89:1598–1604.

Results of Italian Society of Endocrinology specific study group regarding etiologic classification of PAI are presented. Two hundred twenty-two participants were tested for the presence of 21OHAb and adrenal cortex autoantibodies in two independent laboratories. Both antibodies were positive in 57%, 21OHAb only in 8%, and ACA were present in 12% of patients. Fifty patients had negative adrenal antibodies; of these, six had idiopathic etiology of insufficiency (falsely negative antibodies). A comprehensive flowchart for the classification of PAI was developed by authors.

109. (3) **Elfstrom P,** et al. Risk of primary adrenal insufficiency in patients with celiac disease. J Clin Endocrinol Metab 2007;92:3595–3598.

Through Swedish national registers, authors identified 14.3666 individuals with celiac diseases and 70,095 matched controls. Via Cox regression to estimate hazard ratios (HR),

a significant positive association between celiac disease and adrenal insufficiency was found with a follow-up of a minimum of 1 year (HR = 11.4, CI = 4.4–29.6).

110. (1) **Sprung CL,** et al. Hydrocortisone therapy for patients with septic shock. N Engl J Med 2008;358:111–124.

Multicenter, randomized trial, double-blind, placebo-controlled trial of 499 patients with septic shock who were assigned either to receive hydrocortisone 50 mg IV or placebo every 6 hours for 5 days; dose then tapered during 6-day period. Primary outcome, 28-day mortality, revealed no significant difference in patients who did not have a response to corticotropin (46.7% of total patients); 29.2% in hydrocortisone group versus 36.1% placebo, $p = 0.69$, or between those who had a response to corticotropin (28.8% in hydrocortisone group and 28.7% in placebo group). Treated group experienced more superinfections.

111. (2) **Bendel S,** et al. Free cortisol in sepsis and septic shock. Anesth Analg 2008;106:1813–1819.

Prospective study of 125 patients with severe sepsis or shock with mortality of 21%. Nonsurvivors had a higher calculated serum free cortisol and total cortisol concentrations than survivors ($p = 0.02$). Calculated free cortisol correlated well with serum total cortisol.

112. (1) **Annane D,** et al. Corticosteroids in the treatment of severe sepsis and septic shock in adults: a systematic review. JAMA 2009;301:2362–2375.

Meta-analysis of 17 randomized trials ($n = 2138$) and three quasirandomized trials to review 28-day mortality of corticosteroids versus placebo for severe sepsis/septic shock. Treated patients ($n = 1099$) mortality was 35.3% versus placebo 38.5% in randomized trials (RR-0.84, CI 0.71–1.00, $p = 0.05$) of various protocols.

113. (3) **Erturk E,** et al. Evaluation of the integrity of the hypothalamic-pituitary-adrenal axis by insulin hypoglycemia test. J Clin Endocrinol Metab 1998;83:2350–2354.

Retrospective review of ACTH and cortisol responses to insulin hypoglycemia in 193 subjects with suspected ACTH deficiency. Of these, 133 subjects were classified as having an intact hypothalamic–pituitary–adrenal axis, and 60 subjects were determined to have ACTH deficiency based on a cutoff value for peak cortisol of 18 mg/dl. Baseline and peak cortisol concentrations were strongly correlated ($r = 0.63$; $p < 0.0001$). Basal cortisol values more than 17 mg/dl or less than 4 mg/dl were highly predictive of an intact or impaired hypothalamic–pituitary–adrenal axis, respectively, but intermediate values had only limited sensitivity and specificity. An increase in plasma cortisol of more than 7 mg/dl above baseline or doubling of the baseline cortisol value had high false-positive and false-negative rates in predicting integrity of the HPA axis.

114. (3) **Oelkers WS,** et al. Diagnosis and therapy surveillance in Addison's disease: Rapid adrenocorticotropin (ACTH) test and measurement of plasma ACTH, renin activity, and aldosterone. J Clin Endocrinol Metab 1992;75:259–264.

In 45 patients with PIA, results of the rapid ACTH test and single measurements of plasma cortisol, ACTH, aldosterone, and PRA taken between 8 and 9 a.m. were compared with measurements in 55 normal subjects and 46 patients with pituitary disease (cortisol and ACTH only). The rapid ACTH test result was abnormal in all 41 patients who underwent PAI testing. Plasma ACTH, PRA, and the ratios of ACTH to cortisol and PRA to plasma or urinary aldosterone were clearly elevated in all of patients with PAI. The ACTH/cortisol ratio distinguished 100% of patients with PAI from SAI but not control subjects from those with SAI. PRA measurements during treatment with hydrocortisone and fludrocortisone correlated better with the mineralocorticoid dose than did plasma potassium and sodium levels. PRA measurement is a valuable tool in assessing mineralocorticoid therapy.

115. (2) **Abdu T,** et al. Comparison of the low dose short Synacthen test (1 μg), the conventional dose short Synacthen test (250 μg), and the insulin tolerance test for the assessment of the hypothalamo-pituitary-adrenal axis in patients with pituitary disease. J Clin Endocrinol Metab 1999;84:838–843.

Authors prospectively studied 42 patients with suspected or proven pituitary disease and compared results of three tests as described in the title. The low-dose synacthen test was slightly more sensitive than the standard synacthen test (6% of patients had false reassurance with the standard test; with a 30-minute cortisol cutoff as 500 nmol/l (18 μg/dl).

116. (2) **Dorin RI,** et al. Diagnosis of adrenal insufficiency. Ann Intern Med 2003;139:194–201.

Authors generated summary ROC curves from 20 various published studies for standard cosyntropin test and for 9 published low-dose cosyntropin test studies (all identified on MEDLINE database). They further provided sensitivity and specificity results. At a specificity of 95%, sensitivities for SAI diagnosis were 57% and 61% for summary ROC curves in tests for

standard-dose test and low-dose test, respectively. The area under the curve did not differ significantly ($p > 0.5$).

117. (2) **Wade M,** et al. Technical details influence the diagnostic accuracy of the 1 microg ACTH stimulation test. Eur J Endocrinol 2010;162:109–113.

Sixty healthy volunteers underwent LDT in a random fashion either at 8 a.m. or 4 p.m. Specificity of the test was 58%. Further analysis attributed the abnormal results to afternoon testing (sevenfold increase) and loss of cosyntropin in IV tubing.

118. (2) **Schindhelm RK,** et al. Salivary cortisol as an alternative for serum cortisol in the low-dose adrenocorticotropic hormone stimulation test? J Endocrinol Invest 2010;33:92–95.

Consecutive 51 patients who underwent LDT for various indications were studied, and serum cortisol as well as salivary cortisol (30 minutes after Cortrosyn administration) were measured. The salivary cortisol yielded more dynamic response; however, cutoff of 23.5 nmol/l had a sensitivity of 78.1% and specificity of 70% compared to serum cutoff values greater than 0.5 μmol/l.

119. (2) **Alonso N,** et al. Evaluation of two replacement regiments in primary adrenal insufficiency patients: Effect on clinical symptoms, health-related quality of life (HRQL) and biochemical parameters. J Endocr Invest 2004;27:449–454.

Authors prospectively studied two different regiments of hydrocortisone in PAI (20 mg–0 mg–10 mg and 10 mg–5 mg–5 mg), each maintained for 3 months and compared with healthy controls. Patients with adrenal insufficiency had a worse HRQL in the energy dimension compared with the general population, regardless of the treatment regimen. However, the thrice-daily hydrocortisone regiment showed a more physiologic cortisol profile.

120. (3) **Bleicken B,** et al. Impaired subjective health status in chronic adrenal insufficiency: impact of different glucocorticoid replacement regimens. Eur J Endocrinol 2008;159:811–817.

Cross-sectional study of 526 patients with primary or secondary AI treated with hydrocortisone or prednisolone completed three validated self-assessment questionnaires and compared to matched controls. Both groups were found to have significant impairment of subjective health status. Difference in subanalysis of primary AI was higher bodily pain in patients on prednisolone ($p < 0.05$), and in patients with secondary AI, the prednisolone group showed less heart complains ($p \leq 0.05$).

121. (3) **Bergthorsdottir R,** et al. Premature mortality in patients with Addison's disease: a population-based study. J Clin Endocrinol Metab 2006;91:4849–4853.

Retrospective, population-based study of National Swedish Hospital Death Registry identified 1,675 patients with primary AI with average follow-up of 6.5 years. The risk ratio for all-cause mortality was 2.19 (CI 1.91–2.51) for men and 2.86 for women (CI 2.54–3.20) compared to background population.

122. (1) **Arlt W,** et al. Dehydroepiandrosterone replacement in women with adrenal insufficiency. N Engl J Med 1999;341:1013–1016.

Prospective, double-blind, randomized trial in 24 women with PAI regarding dehydroepiandrosterone replacement (50 mg orally daily) for 4 months with a 1-month washout. Treatment with dehydroepiandrosterone improved overall well-being as well as scores for depression and anxiety and sexuality.

123. (1) **Dhatariya K,** et al. Effect of dehydroepiandrosterone replacement on insulin sensitivity and lipids in hypoadrenal women. Diabetes 2005;54:765–770.

This was a randomized, double-blind, placebo-controlled, crossover study in 28 hypoadrenal women receiving a 50-mg dose of dehydroepiandrosterone. After 12 weeks, insulin sensitivity (assessed by hyperinsulinemic–euglycemic clamp) was increased ($p < 0.05$), and levels of total cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol were reduced ($p < 0.05$).

124. (1) **Lovas K,** et al. Replacement of dehydroepiandrosterone in adrenal failure: No benefit for subjective health status and sexuality in a 9-month, randomized, parallel group clinical trial. J Clin Endocrinol Metab 2003;88:112–1117.

Prospective, randomized trial of dehydroepiandrosterone replacement (25 mg orally daily) in 39 women with adrenal failure. No difference in subjective health scales was found between the placebo and treatment groups. Androgenic side effects were seen in 89% of the dehydroepiandrosterone group.

125. (1) **Alkatib AA,** et al. A systematic review and meta-analysis of randomized placebo-controlled trials of DHEA treatment effects on quality of life in women with adrenal insufficiency. J Clin Endocrinol Metab 2009;94:3676–3681.

Meta-analysis of 10 eligible trials of thin women with primary or secondary AI who received DHEA versus placebo. It showed a small improvement in HRQL (effect size 0.21; 95%

CI 0.08–0.33, inconsistency = 33%). There was a small beneficial effect of DHEA on depression, effect on anxiety and sexual well-being were also small and not statistically significant.

Pheochromocytoma

126. (2) **Young WF Jr.** Pheochromocytoma and primary aldosteronism: Diagnostic approaches. Endocrinol Metab Clin North Am 1997;26:801–827.

    This is an excellent overview of the current diagnosis and treatment of pheochromocytoma.

127. (1) **Januszewicz W, Wocial B.** Pheochromocytoma: The catecholamine-dependent hypertension. J Physiol Pharmacol 1995;46:285–295.

    A comprehensive review of the physiology of catecholamine synthesis and pheochromocytoma

128. (1) **Pacak K,** et al. Recent advances in genetics, diagnosis, localization, and treatment of pheochromocytoma. Ann Intern Med 2001;134:315–329.

    This reference provides an excellent summary of the recent advances in genetic testing for pheochromocytoma.

129. (2) **Manger WM,** Gifford RW Jr. Pheochromocytoma: Current diagnosis and management. Cleve Clin J Med 1993;60:365–378.

    The reference reviews the current patient evaluation of pheochromocytoma. Pheochromocytoma can mimic several other diseases, making recognition difficult. Hypertension may be paroxysmal or sustained. The signs and symptoms of pheochromocytoma are mostly due to hypercatecholaminemia, hypertension, complications, or coexisting diseases; however, measurements of catecholamines and their metabolites in the plasma and urine may be normal between attacks, and other conditions can elevate these values. The clonidine suppression test confers specificity to the clinical and laboratory findings, and MRI is the most reliable method of locating a tumor. Surgical resection is successful in 90% of patients; however, the disease is fatal if it is not detected and treated. Pheochromocytoma should be suspected in patients with paroxysmal or sustained hypertension, particularly if symptoms are present.

130. (2) **Adler JT,** et al. Pheochromocytoma: Current approaches and future directions. The Oncologist 2008;13:779–793.

    Excellent review of current medical and surgical literature addressing all present and future directions in the evaluation and management of pheochromocytoma

131. (2) **Omura M,** et al. Prospective study on the prevalence of secondary hypertension patients visiting a general outpatient clinic in Japan. Hypertens Res 2004;27:193–202.

    This study investigates the incidence of pheochromocytoma in random patients with hypertension.

132. (1) **Lo CY,** et al. Adrenal pheochromocytoma remains a frequently overlooked diagnosis. Am J Surg 2000;179:212–215.

    This study documents the delay in diagnosis of pheochromocytoma in many patients and incidence of these tumors in autopsy series.

133. (1) **Modigliani E,** et al. Pheochromocytomas in multiple endocrine neoplasia type 2: European study: The European Study Group. J Intern Med 1995;238:363–367.

    This reference describes the unique characteristics and genetic testing of pheochromocytomas occurring in patients with the MEN2 syndrome.

134. (2) **Sheps SG,** et al. Recent developments in the diagnosis and treatment of pheochromocytoma. Mayo Clin Proc 1990;65:88–95.

    This reference describes the clinical presentation of a patient with pheochromocytoma. Recent clinical developments include the detection of asymptomatic paroxysms of hypertension by 24-hour ambulatory monitoring, detailed characterization of catecholamine cardiomyopathy by echocardiography, and further experience with Carney triad and other polyglandular and multiple neoplasia syndromes associated with pheochromocytoma. Refinement in interpretation of catecholamine measurements and the development of radionuclide scanning with *m*-[^{131}I]iodobenzylguanidine, CT, and MRI have greatly enhanced clinicians' diagnostic acumen. Developments in antihypertensive drug therapy and chemotherapy have improved management of catecholamine hypersecretion and tumor growth, respectively, in inoperable patients and in the preparation of patients for anesthesia and surgical treatment. Flow cytometry to detect abnormal DNA histograms may prove particularly useful in predicting the malignant nature of the tumors.

135. (1) **Nativ O,** et al. The clinical significance of nuclear DNA ploidy pattern in 184 patients with pheochromocytoma. Cancer 1992;69:2683–2687.

    This article describes aspects of malignancy determination in patients with pheochromocytoma by using flow cytometry: Flow-cytometric nuclear DNA analysis was performed on

paraffin-embedded tissue samples taken from 184 patients with pheochromocytoma and paraganglioma treated between 1960 and 1987. Hedley's technique was used for measurement of nuclear DNA content. About 35% of the tumors were DNA diploid, 33% showed a DNA tetraploid pattern, and 32% had a DNA aneuploid pattern. Familial pheochromocytoma and associated endocrine or neoplastic disorders were more common among patients with DNA nondiploid tumors. Eighty-four percent of the tumors that invaded blood vessels and all patients with regional or distant metastases were associated with tumors that were classified as DNA tetraploid or DNA aneuploid. Of 22 patients who had disease progression, 21 (95%) had tumors with abnormal DNA ploidy pattern ($p < 0.001$). All 12 patients who died of cancer-related disease had abnormal DNA ploidy; none of the 64 patients with DNA diploid tumor has died as a result of pheochromocytoma ($p < 0.01$). These results suggest that nuclear DNA ploidy pattern is an important and independent prognostic variable for patients with pheochromocytoma and paraganglioma.

136. (1) **Batide-Alanore A,** et al. Diabetes as a marker of pheochromocytoma in hypertensive patients. J Hypertens 2003;21:1703–1707.

This study focuses on the incidence of pheochromocytoma in patients with diabetes and hypertension.

137. (1) **Mansmann G,** et al. The clinically inapparent adrenal mass: Update in diagnosis and management. Endocr Rev 2004;25:309–340.

This review focuses on the detection and incidence of pheochromocytoma in incidentally discovered adrenal masses. It provides a logical strategy for the evaluation and management of these tumors in this clinical setting.

138. (2) **Lairmore TC,** et al. Management of pheochromocytoma in patients with multiple endocrine neoplasia type 2 syndromes. Ann Surg 1993;217:595–601.

This article provides advice and recommendations for the treatment of pheochromocytoma in the context of the MEN2 syndrome. The results of unilateral or bilateral adrenalectomy were studied in 58 patients (49 with MEN2A and nine with MEN2B). Recurrence of disease was evaluated by measuring 24-hour urinary excretion rates of catecholamines and metabolites and by CT scanning. In a mean postoperative follow-up of 9.4 years, no operative mortality occurred; malignant or extra-adrenal pheochromocytomas were not present. Twenty-three patients with a unilateral pheochromocytoma and a macroscopically normal contralateral gland underwent unilateral adrenalectomy. A pheochromocytoma developed in the remaining gland a mean duration of 11.87 years after the primary adrenalectomy in 12 (52%) patients. Conversely, pheochromocytoma did not develop in 11 (48%) patients during a mean interval of 5.18 years. In the interval after unilateral adrenalectomy, no patient experienced hypertensive crises or other complications related to an undiagnosed pheochromocytoma. Ten (23%) of forty-three patients who earlier had both adrenal glands removed (either at a single operation or sequentially) experienced at least one episode of acute adrenal insufficiency or addisonian crisis, including one patient who died during an episode of influenza. Based on these data, the treatment of choice for patients with MEN2A or MEN2B and a unilateral pheochromocytoma is resection of only the involved gland. Substantial morbidity and significant mortality are associated with the addisonian state after bilateral adrenalectomy.

139. (2) **Lenders JWM,** et al. Plasma metanephrines in the diagnosis of pheochromocytoma. Ann Intern Med 1995;123:101–109.

This reference reviews the methods of detecting catecholamine excess by measuring urinary and plasma catecholamines. Results show that normal plasma concentrations of metanephrines rule out the diagnosis of pheochromocytoma, whereas normal plasma concentrations of catecholamines and normal urinary excretion of metanephrines do not. Tests for plasma metanephrines are more sensitive than tests for plasma catecholamines or urinary metanephrines for the diagnosis of pheochromocytoma.

140. (1) **Lenders JW,** et al. Biochemical diagnosis of pheochromocytoma: Which test is best? JAMA 2002;287:1427–1434.

In this multicenter cohort study, findings in 214 patients with confirmed pheochromocytoma were compared with those of 644 normal patients. The sensitivities and specificities of the tests undertaken were plasma free metanephrines, 99% and 89%; urinary fractionated metanephrines, 97% and 69%; plasma catecholamines, 84% and 81%; urinary catecholamines, 86% and 88%; and urinary total metanephrines, 77% and 93%, respectively.

141. (2) **Lenders JWM,** et al. Phaeochromocytoma. Lancet 2005;366:665–675.

This reference is an excellent review of all the most recent articles published from 2000 to 2005 on the subject of pheochromocytoma. The information was extracted from a database review of PubMed and EMBASE and includes book chapters, review articles, and commonly referenced new and older publications.

142. (1) **Bravo EL,** et al. Clonidine-suppression test: A useful aid in the diagnosis of pheochromocytoma. N Engl J Med 1981;305:623–626.

143. (1) **Eisenhofer G,** et al. Biochemical diagnosis of pheochromocytoma: How to distinguish true from false-positive test results. J Clin Endocrinol Metab 2003;88:2656–2666.

This study included 208 patients with pheochromocytoma and 648 patients in whom pheochromocytoma was excluded and assessed medication-associated false-positive results and use of supplementary tests, including plasma normetanephrine responses to clonidine, to distinguish true- from false-positive results.

144. (1) **Plouin PF,** et al. Factors associated with perioperative morbidity and mortality in patients with pheochromocytoma: analysis of 165 operations at a single center. J Clin Endocrinol Metab 2001;86:1480–1486.

This study identified preoperative factors in 147 patients associated with 30-day morbidity and mortality after pheochromocytoma surgery. Patients with high secretion tumors and those undergoing repeat intervention are at high risk of complications and should be referred to centers familiar with pheochromocytoma management.

145. (2) **Bravo EL.** Pheochromocytoma: An approach to antihypertensive management. Ann N Y Acad Sci 2002;970:1–10.

This study reviews the pathophysiologic mechanisms that sustain the hypertension and the pharmacology of antihypertensive agents for patients with pheochromocytoma to allow better selection of antihypertensive therapy.

146. (3) **Kinney MA,** et al. Perioperative management of pheochromocytoma. J Cardiothorac Vasc Anesth 2002;16:359–369.

This review article outlines the preoperative preparation and intraoperative anesthetic and pharmacologic management of patients with known pheochromocytoma.

This study provides the details and usefulness of the clonidine-suppression test to identify patients with pheochromocytoma.

147. (1) **Varghese JC,** et al. MR differentiation of phaeochromocytoma from other adrenal lesions based on qualitative analysis of T2 relaxation times. Clin Radiol 1997;52:603–606.

This article reviews the imaging of pheochromocytoma and describes specific techniques using MRI to distinguish pheochromocytomas from other functional and nonfunctional adrenal tumors. It concludes that considerable overlap exists between the MRI appearance of pheochromocytoma and other adrenal lesions. A pheochromocytoma cannot be excluded on the basis of a lack of high signal intensity on T2-weighted MRI.

148. (2) **Gagner M,** et al. Is laparoscopic adrenalectomy indicated for pheochromocytoma? Surgery 1996;120:1076–1080.

This study examined the safety and efficacy of laparoscopic adrenalectomy for patients with pheochromocytoma. Based on 90 laparoscopic adrenalectomies performed in 82 patients, the authors concluded that laparoscopic adrenalectomy for pheochromocytoma is difficult because tumors are larger and more complications are seen related to their hormonal secretions, despite adequate pharmacologic blockade. However, metastatic extensions can be diagnosed and laparoscopic ablation can be performed in most instances without recurrence. It is not, therefore, a contraindication for this approach.

149. (3) **Amar L,** et al. Year of diagnosis, features at presentation, and risk of recurrence in patients with pheochromocytoma or secreting paraganglioma. J Clin Endocrinol Metab 2005;90:2110–2116.

This study outlines the demographics of patients found to have a pheochromocytoma and focuses on the significant delay in diagnosis in many patients with this disorder.

150. (3) **Pacak K,** et al. Radiofrequency ablation: A novel approach for treatment of metastatic pheochromocytoma. J Natl Cancer Inst 2001;93:648–649.

This case report illustrates that RFA can be used safely to ablate rapidly growing pheochromocytoma.

151. (3) **Takahashi K,** et al. Malignant pheochromocytoma with multiple hepatic metastases treated by chemotherapy and transcatheter arterial embolization. Intern Med 1999;38:349–354.

This case report describes the utility of transcatheter arterial embolization for multiple hepatic metastases under careful blood pressure monitoring.

152. (1) **Rose B,** et al. High-dose ^{131}I-metaiodobenzylguanidine therapy for 12 patients with malignant pheochromocytoma. Cancer 2003;98:239–248.

This reference provides information regarding a small group of patients treated with high-dose radiolabeled MIBG in patients with extensive metastatic disease from malignant

pheochromocytoma. The use of this agent is modestly successful in controlling catecholamine production for these patients over a short period in a palliative setting.

153. (2) **Shapiro B,** et al. Radioisotope diagnosis and therapy of malignant pheochromocytoma. Trends Endocrinol Metab 2001;12:469–475.

This reference discusses the radiopharmaceuticals presently employed in malignant pheochromocytoma for both diagnostic and therapeutic uses and potential future compounds that may find their way into clinical practice in the approach to these and other related neoplasms.

4

Metabolic Bone Disorders

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EVALUATION OF METABOLIC BONE DISORDERS

As with any disease, the workup of metabolic bone disorders starts with a comprehensive history and physical examination. Diagnosis of these disorders is usually made based on clinical history, results of biochemical tests, and radiologic studies.

Serum Calcium, Phosphate, and Magnesium

In patients with normal albumin concentrations, serum calcium is usually accurate. However, with abnormal albumin levels, the formula for their correction may be inaccurate in 20% to 30% of cases. In this case, one should obtain an ionized calcium measurement. Phosphate levels are useful in the evaluation of hypocalcemia and hypercalcemia. Magnesium levels should be checked in the workup of hypocalcemia because low magnesium may decrease parathyroid hormone (PTH) secretion or lead to resistance to its effects.

Intact Parathyroid Hormone

The most reliable measure of PTH status is the intact molecule. Radioimmunoassay (RIA) is most commonly used, but two-site immunologic assays using immunoradiometric assay (IRMA) or colorimetric/chemiluminescence detection also are available. A new assay, bio-intact PTH, eliminates the effect of PTH fragments that build up in renal failure.

Vitamin D Metabolites

The two clinically useful metabolites are 25(OH)D, or calcidiol, and 1,25(OH)D, or calcitriol.

The methodology used to assess 25(OH)D status can lead to substantial variability in serum vitamin D measurements. Currently, there is no internationally recognized primary standard for 25(OH)D measurement. High-performance liquid chromatography (HPLC) has been recognized as the gold standard for the measurement of 25(OH)D; however, it is not widely available to clinicians.

Chemiluminescent assay is a protein-binding assay that uses a multistep procedure to measure 25(OH)D. It is important to note that different assays may use different sources of vitamin D–binding proteins, and the method of extraction/purification may vary between assays, which can lead to different results based on the competitive protein assay used. A more reliable method to measure 25(OH)D is to use RIA methodology, which has become the most commonly used method. This method uses antibodies to measure 25(OH)D, and the measurements correlate with values obtained by HPLC.

1,25(OH)D is the active form of vitamin D and can be measured using RIA. 1,25(OH)D levels may not be reliable in vitamin D–deficiency states, because stimulation of 1α-hydroxylation of 25(OH)D in secondary hyperparathyroidism can increase this concentration.

Parathyroid Hormone–Related Protein

Compared with PTH, PTH-related protein (PTHrP) is a larger molecule. They share many N-terminal homologues but few C-terminal sequence homologues. In addition, both share the same receptor. PTHrP is elevated in 60% to 80% of patients with hypercalcemia due to ectopic secretion of PTHrP.

Calcitonin

This is used mainly for diagnosis and follow-up of medullary carcinoma. Sensitivity for calcitonin increases with stimulation by pentagastrin or calcium.

Urinary Calcium Excretion

Normal calcium excretion usually falls in the range of 1.5 to 4.0 mg of calcium/kg body weight per 24 hours. Most calcium-replete women have levels in the range of 150 to 250 mg/24 hr, while men have levels up to 300 mg/24 hr. A simultaneous urine creatinine should be measured to ensure complete collection. Measurement of urinary sodium is also important as high sodium intake leads to an increase in urinary sodium excretion, which in turn enhances urinary calcium excretion. The fractional excretion of calcium is calculated by using the following formula: (urinary calcium × serum creatinine)/(urinary creatinine × serum calcium).

Biochemical Markers of Bone Turnover

Bone-turnover markers (BTMs) can provide information regarding the dynamic state of the bone. While they are not used for screening and diagnosis of osteoporosis, they can be helpful for risk assessment as well as for monitoring response to therapy.

Bone-Formation Markers

Osteocalcin and bone-specific alkaline phosphatase (BSAP) are the most commonly used measures of bone formation. Of note, osteocalcin also reflects bone resorption because it is released into the circulation from the matrix during this process. BSAP is produced by osteoblasts and is an enzyme necessary for bone mineralization. BSAP is not affected by the circadian rhythm and therefore more convenient to measure. Other markers of bone formation are carboxy- and amino-terminal propeptide of type 1 collagen (PICP and PINP).

Osteoprotegerin (OPG) inhibits RANKL and subsequent osteoclast production. Estrogen and raloxifene enhance its concentration, whereas corticosteroids inhibit it. However, OPG is not specific for bone, and its concentration is affected by disease processes such as renal failure; this limits its clinical utility as a bone marker [1].

Bone-Resorption Markers

Urinary levels of N- and C-telopeptide of collagen cross-links (NTX and CTX), free and total pyridinolines (Pyd), free and total deoxypyridinolines (Dpd), and hydroxyproline are used as markers of bone resorption. Urinary NTX and CTX

are the most commonly used in clinical practice. RANKL, briefly mentioned earlier, is a ligand that, on binding to its receptor RANK, stimulates osteoclast production and inhibits osteoclast destruction. A negative association between RANKL and 17β-estradiol and a positive correlation between RANKL and bone-resorption markers have been noted. RANKL is the target of more recent treatments for osteoporosis [1].

Acid phosphatases are lysosomal enzymes present in osteoclasts. There are six isoenzymes with tartrate-resistant acid phosphatase 5b (TRACP5b) predominating in the bone. TRACP5b is the only osteoclast-specific product, and it has low diurnal variation. This marker has been studied to assess response to antiresorptive treatment, but more studies are needed to elucidate the clinical role of this bone marker.

Similarly, the role of cathepsin K (CTSK; a lysosomal cysteine protease expressed in osteoclasts) as a marker of bone resorption has been studied, but more data are necessary to evaluate its clinical utility.

Clinical Use

Because of the diurnal variation and technical variability of these markers, controversy remains as to their routine use in osteoporosis management. Long-term variability can vary by as much as 20% to 30% for urine markers and 10% to 15% for serum markers [2,3]. Obtaining a 24-hour urine collection for bone markers may help avoid circadian variations. However, other factors such as diet, muscle mass, and kidney function can also affect BTMs.

Keeping in mind some of the limitations, bone markers have an increasing role in the management of osteoporosis. They are useful in predicting bone loss, fracture risk, and response to therapy.

In one study, the serial assessment of BTMs over a 5-year period identified women, who were not on pharmacologic treatment for bone loss, at highest risk for bone loss and osteoporosis [4]. In another study, baseline degrees of NTX elevation and the subsequent degrees of suppression predicted bone mineral density (BMD) gains in subjects receiving hormone replacement therapy (HRT) [5]. This association was also demonstrated in patients taking alendronate [6].

Studies have shown that elevated levels of BTMs lead to an increase in the relative risk of fractures independent of BMD and physical performance. Studies have shown that the relationship between BTMs and risk of fracture is not linear, and women with BTMs in the highest quartile had the higher risk of fracture [7,8]. However, not all studies have shown this association.

The most widely accepted use of bone markers is in determining medication compliance and efficacy of antiresorptive therapy. For this purpose, they are usually obtained before and 3 to 6 months after initiation of treatment and during subsequent follow-up. A decline in bone-resorption markers can be seen with antiresorptive agents and increases seen with anabolic therapy.

A meta-analysis showed that larger reduction in BTMs was associated with a greater reduction in risk of nonvertebral fractures (70% reduction in markers of bone resorption reduced the risk of fracture by 40%, and 50% reduction in bone-formation markers reduced the risk by 44%) in patients treated with antiresorptive agents [9]. In the Fracture Intervention Trial (FIT), women treated with alendronate who had at least a 30% decline in BSAP had a greater risk reduction (RR) in risk of spine, nonspine, and hip fractures compared to those with less than 30% decline [10].

BONE IMAGING

Classic radiographic findings in common metabolic bone diseases are shown in Table 4.1.

Table 4.1. Features of Common Metabolic Bone Diseases

Disease	Radiograph	Bone Scan
Osteoporosis	Decreased bone density, cortical thinning, end-plate vertebral deformities, wedging, and compression fractures	Useful in differentiating old and new vertebral fractures. New fractures appear as hot areas.
Osteomalacia	Decreased bone density, indistinct borders between cortex and trabeculae, widened growth plates, bowing deformities, and stress fractures	Increased activity in axial skeleton, long bones, mandible and calvaria, costochondral junction
Primary hyperparathyroidism	Subperiosteal resorption, thinning of distal third of the clavicle, salt-and- pepper appearance of the skull, brown tumors, osteitis fibrosa cystica, and decreased bone density	Most show no abnormalities. Fractures may be detected. There can be increased activity in the axial skeleton.
Paget disease	Increased cortical thickness, irregular areas of bony sclerosis	Increased uptake in affected areas, flame- or V-shaped in the advancing edge; involvement of whole bone

Bone Densitometry

BMD is an important part of evaluation and management of osteopenia and osteoporosis. BMD can be measured with different techniques. The most commonly used method is dual-energy x-ray absorptiometry (DXA), which gives a precise measure of a real density of bone (expressed in grams of mineral per square centimeter). The *T*-score compares an individual's BMD to the mean for younger controls, and the difference is reported as a standard deviation (SD). The Z-score compares an individual's BMD to the mean for the gender- and age-matched population. *T*-scores are used for defining osteoporosis, and *Z*-scores provide an idea of the "age appropriateness" of bone loss. The preferred sites for measuring BMD include the hip and the spine. The bone density of the distal one-third radius can be utilized if the hip or the spine BMD cannot be obtained or in certain clinical settings such as in patients with primary hyperparathyroidism (PHPT). While BMD of other peripheral sites such as the calcaneus or the finger can also be measured, there is no standard reference *T*-scores for peripheral DXA with the exception of the distal one-third radius.

The World Health Organization (WHO) classification is widely used for the diagnosis of osteoporosis (Table 4.2). For each SD decrease in BMD, fracture risk increases 1.5- to 3-fold [11]. The National Health and Nutrition Examination BMD III (NHANES III) database provides standardized total hip and femoral

Table 4.2. WHO Criteria for the Diagnosis of Osteoporosis

Classification	*T*-Score
Normal	−1 to 1
Osteopenia	−1 to −2.4
Osteoporosis	−2.5 or less
Severe osteoporosis	−2.5 or less, with fragility fractures

neck BMD values for men, white women, and nonwhite women. The use of the NHANES database eliminates manufacturer-specific database variabilities.

The DXA scan also provides a reliable and objective means with which to monitor the response to osteoporosis therapy. The precision error of most DXA machines ranges from 0.5% to 2.5%, and the "least significant change", or the change in bone density considered to be statistically significant, is at least 2.8 times the precision error of the machine. Abnormalities of the bone, such as degenerative joint disease and vertebral compression fractures, can falsely elevate the BMD. This is commonly seen in the spines of elderly individuals.

The International Society of Clinical Densitometry does not recommend using the lateral spine for diagnosing osteoporosis because it is thought to overestimate the disease. The lateral view, however, is useful in assessing for vertebral fragility fractures especially in patients who are at higher risk of fractures such as those with unexplained height loss, kyphosis, or in patients on long-term glucocorticoid therapy. A study of 342 patients who underwent DXA scanning with lateral vertebral views found compression fractures in 14.6% of these patients. In this trial, 73 (21.3%) of the 342 patients were at least 60 years old and osteopenic, and almost 28% of these subjects had compression fractures [12]. Lateral vertebral analysis is increasingly being used to identify prevalent vertebral fractures and to guide clinicians in the initiation of therapy. In addition, degenerative changes that are commonly seen in the posteroanterior view are usually absent from the lateral view.

Scintigraphy

The most commonly used radiolabeling compound is technetium 99m (^{99m}Tc). The availability of single-photon emission computed tomography has improved detection of vertebral fractures, but it is most useful in the detection of metastatic bone disease and in the localization of Paget disease.

Quantitative Computed Tomography

Quantitative computed tomography (QCT) measures volumetric trabecular and cortical bone density. While QCT data can predict risk of fractures, it is not recommended for screening as it has not been validated the same way DXA has been to predict risk of fracture. Also, QCT is associated with higher radiation exposure compared to DXA. It may be useful as a tool in patients who are unable to be assessed by DXA given weight limitations.

Micro–Computed Tomography

More recently, a three-dimensional reconstruction of micro-CT images have been used to evaluate bone microarchitecture; however, currently, QCT is not readily available and is mainly utilized in research and academic institutions.

Quantitative Ultrasound

Quantitative ultrasound (QUS) does not measure BMD but provides information regarding broadband ultrasound attenuation and stiffness index. The measurement is most commonly made at the calcaneus. Studies have shown that

QUS can predict risk of hip fractures. However, it is not used for diagnosing osteoporosis since diagnostic classification criteria have not been established for QUS.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is commonly used to assess the musculoskeletal system. There are studies that have utilized MRI to assess bone density; however, MRI is not routinely used to assess bone density.

Bone Biopsy

Rarely used in clinical practice, bone biopsies can help in the diagnosis of osteomalacia, and they are useful in renal osteodystrophy. They are also used in trials evaluating new osteoporosis drugs, allowing measurement of changes in cortical and trabecular thickness and estimates of structural competence.

OSTEOPOROSIS

Definition

Osteoporosis is a disease characterized by decreased bone strength due to decreased bone density and bone quality, leading to increased bone fragility. The WHO definition of osteoporosis is outlined in Table 4.2.

Epidemiology

Based on the National Health and Nutrition Survey III (NHANES III), the National Osteoporosis Foundation (NOF) estimates that more than 33.6 million Americans have low bone density of the hip and more than 10 million Americans have osteoporosis. Approximately one in two Caucasian women and one in five men will experience an osteoporotic-related fracture in their lifetime. Hip fractures are one of the most serious complications of osteoporotic fractures. Hip fractures impair mobility and are associated with a higher mortality rate during the 1st year after fracture (30% in men and 17% in women). It is estimated that by the year 2025, the number of osteoporosis-related fractures will increase to 3 million.

Pathophysiology

Bone mass is determined by the peak bone density achieved in early adulthood and the subsequent balance between bone formation and bone resorption in adulthood. Both genetics and dietary factors play a role in reaching peak bone density. A higher rate of bone resorption compared to bone formation will lead to bone loss. Some factors that can lead to predominance of bone resorption are listed in Table 4.3.

Diagnosis

Initial history and physical examination should include assessment of risk factors for fractures as well as secondary causes of osteoporosis. The FRAX tool aims to merge both risk factors and BMD data to better assess risk of fracture. The risk factors included in FRAX are listed in Table 4.4. However, not all risk factors for osteoporosis are included in FRAX (see Tables 4.3 and 4.5). The most commonly encountered secondary causes of osteoporosis are detailed in Table 4.3. General recommendations for obtaining a screening DXA scan are outlined in Table 4.6. Despite the many advances over the years, many cases of osteoporosis go undiagnosed and a significant number of patients with osteoporosis do not receive the appropriate treatment.

Prevention

The American Association of Clinical Endocrinologists (AACE) 2010 guidelines recommend the following measures to prevent bone loss: adequate calcium and vitamin D intake (to maintain 25 OHD levels between 30 and 60 ng/ml), less than two servings of alcohol per day, limiting caffeine intake, smoking cessation, and maintaining an active lifestyle (30 minutes of weight-bearing exercise a day).

Table 4.3. Secondary Causes of Osteoporosis

Endocrine
- Hyperparathyroidism
- Hypophosphatasia
- Growth hormone deficiency
- Hypercortisolism
- Diabetes
- Adrenal insufficiency
- Hypogonadism
- Hyperthyroidism

Nutritional and Gastrointestinal Conditions
- Vitamin D deficiency
- Calcium deficiency
- High caffeine intake
- Anorexia nervosa
- Alcoholism
- Chronic liver disease
- Malabsorption (inflammatory bowel diseases, celiac sprue, pancreatic disease, gastric resection or bypass)

Medications
- Glucocorticoids
- Aromatase inhibitors
- Gonadotropin-releasing hormone agonists
- Lithium
- Depo-Provera
- Chemotherapy and immunosuppressants
- Antiepileptics (phenobarbital, phenytoin, carbamazepine, valproate, primidone)
- Anticoagulants (heparin and coumadin)
- Thiazolidinediones
- Proton pump inhibitors
- Thyroid hormone overreplacement

Connective Tissue Disorders
- Osteogenesis imperfecta
- Marfan syndrome
- Ehlers-Danlos syndrome

Hematologic Disorders
- Multiple myeloma
- Leukemia and lymphoma
- Hemophilia
- Sickle cell disease
- Thalassemia
- Systemic mastocytosis

Miscellaneous
- Idiopathic hypercalciuria
- Immobilization
- Low physical activity
- Rheumatoid arthritis
- Chronic obstructive pulmonary disease
- Chronic kidney disease
- Congestive heart failure
- Human immunodeficiency virus and acquired immunodeficiency syndrome

Fracture Risk Assessment

Pharmacologic therapy is indicated in patient with *T*-scores in the osteoporotic range and those with history of fragility fracture. However, it is more challenging to identify patients with osteopenia who would benefit from pharmacologic therapy. It is important to note that majority of fractures occur in patients with osteopenia (*T*-score between −1.0 and −2.5), as patients with osteopenia outnumber those with osteoporosis. In 2008, the WHO task force introduced the fracture risk assessment tool known as FRAX. This tool allows for estimating the 10-year probability of major osteoporotic fracture (defined as clinical vertebral, hip, or forearm fracture) and hip fracture. This tool helps identifying postmenopausal women and men over the age of 50 who are at high risk for fracture. It is intended for assessment of patients who have not received prior pharmacotherapy for treatment of osteopenia or osteoporosis. Country-specific

and race-specific data are available for FRAX. The data necessary to use the FRAX tool include patient's age, weight, height, gender, history of previous fracture, history of hip fracture in a parent, tobacco and glucocorticoid use, history of rheumatoid arthritis (RA), and alcohol intake (Table 4.4). The patient's femoral neck BMD can be used (or total hip BMD) if the make of DXA scanning machine is available, otherwise the *T*-score can be used. The FRAX tool does inquire about the presence of secondary causes of osteoporosis; however, this factor does not contribute to the risk assessment as the effect of this variable is already reflected in the BMD. When using the FRAX tool, pharmacologic intervention is recommended for patients with greater than or equal to 20% probability of major osteoporotic fracture or greater than or equal to 3% probability of hip fracture in the next 10 years. While FRAX provides a proposed threshold for initiating therapy, the physician's clinical judgment and individual patient risk factors should always be considered prior to making management decisions.

Treatment

The major guidelines recommend the treatment of patients with history of hip or vertebral fracture, *T*-score less than or equal to −2.5 at the femoral neck (total hip) or spine (after ruling out secondary causes of osteoporosis) or patients with osteopenia with greater than or equal to 20% probability of major osteoporotic fracture or greater than or equal to 3% probability of a hip fracture in the next 10 years based on FRAX tool.

Secondary causes of osteoporosis should be sought and corrected. Preventive therapy, with calcium and vitamin D supplements, and antiresorptive therapy are warranted among patients on chronic glucocorticoid therapy (>5 mg of prednisone daily, or its equivalent, for >3 months).

Table 4.4. FRAX Tool

Age (model accepts ages 40–90; if age is below or above this, the probability is calculated based on age 40 or 90, respectively)
Sex
Weight (kg)
Height (cm)
Previous fracture (occurring during adult life, occurring spontaneously, or low-trauma fracture)
Parental history of hip fracture
Current smoking
Glucocorticoid use (defined as oral glucocorticoids for more than 3 mo at a dose of prednisone ≥ 5 mg/d, or equivalent dose of other glucocorticoids)
Rheumatoid arthritis
Secondary osteoporosis (including type 1 DM, osteogenesis imperfect, untreated longstanding hyperthyroidism, hypogonadism or premature menopause, chronic malnutrition or malabsorption, and chronic liver disease)
Alcohol use (≥3 units of alcohol per day, the definition of a unit of alcohol depends on the country ranging from 8-10 grams of alcohol)
Femoral neck BMD (or *T*-score)*

*Total hip BMD or *T*-score can be substituted if femoral neck data are not available. The field can be left blank if no data is available

Bisphosphonates

Bisphosphonates are the most commonly used class of medication for treatment of osteoporosis. These pyrophosphate analogues bind to hydroxyapatite crystals in the bone, inhibit function and recruitment of osteoclasts, and increase osteoclast apoptosis. Oral bioavailability is only 1% to 3%, but they have prolonged skeletal retention. Patients must be advised to take this medication in the morning, to withhold food and drinks to ensure good absorption, and to remain upright for at least 30 minutes. Erosive esophagitis and gastric ulcers can be caused by these agents.

The three oral bisphosphonates that are approved for the management of osteoporosis are alendronate (Fosamax), risedronate (Actonel), and ibandronate (Boniva).

Alendronate

Alendronate is Food and Drug Administration (FDA) approved for prevention and treatment of postmenopausal osteoporosis, treatment of osteoporosis in men, and treatment of glucocorticoid-induced osteoporosis (GIO). This drug is available in 5-, 10-, 35-, and 70-mg tablet forms. The 70-mg tablet is also available with 2,800 or 5,600 IU of cholecalciferol. Prevention dose is 5 mg once daily or 35 mg once weekly, and treatment dose is 10 mg once daily or 70 mg once weekly. The FIT was the landmark study that established the efficacy of alendronate for the treatment of postmenopausal osteoporosis [13,14]. After 3 years of taking alendronate, those without prior vertebral fractures had a 47% reduction in new radiographic vertebral fractures, a 55% reduction in clinical vertebral fractures, a 90% reduction in multiple vertebral fractures, and a 51% reduction in hip fractures [13]. Those with prior vertebral fractures experienced a 44% reduction in new radiographic vertebral fractures [14]. Mean increases in BMD were 6% to 8% for the lumbar spine (LS) and 4% to 5% for the hip [13,14]. Similar fracture reduction and BMD benefits were seen in two meta-analyses on alendronate for postmenopausal osteoporosis [15,16].

The follow-up to the FIT trial was the Fracture Intervention Trial Long-Term Extension (FLEX), which examined the effect of treatment with alendronate for 10 years compared to 5 years of treatment followed by 5 years of placebo. This was a randomized, double-blind, placebo-controlled study of 1,099 women who received alendronate during the FIT trial. The patients who were continued on alendronate for 5 additional years maintained BMD at the total hip compared with placebo (mean difference of 2.36%, $p < 0.001$). The mean difference in femoral neck BMD was 1.94% ($p < 0.001$). LS BMD increased by 5.26% in the alendronate group compared with 1.52% in the placebo group (mean difference of 3.74%, $p < 0.001$). There was a significantly higher increase in BMD at each site after 10 years of alendronate compared to 5 years of alendronate followed by 5 years of placebo.

BTMs remained stable during the FLEX trial in the group who continued alendronate while BTMs gradually increased over the 5-year study period in the placebo group (however, they remained lower than the FIT baseline values). The effect of alendronate on fracture risk was an exploratory aim. There was no significant difference between the groups for *all* clinical fractures or nonvertebral fractures. However, the risk of clinical vertebral fractures was significantly lower in those who received alendronate (2.4% in the alendronate group vs. 5.3% in the placebo group, a relative RR of 55%). It is important to note that even in those who discontinued alendronate after 5 years, both BMD and BTMs remained above baseline values from 10 years earlier suggesting residual effect of alendronate [17].

A comparison study of 70 mg weekly, 35 mg twice weekly, and 10 mg daily doses of alendronate over a 1-year period revealed similar increases in LS BMD (range, 5.1%–5.4%) in these three groups without observed differences in the side-effect profile [18].

Table 4.5. Fracture Risk Assessment for Osteoporosis

Postmenopausal State	Decreased vision
Advanced age*	Poor balance
Family history of osteoporosis or fractures*	Need for hands to stand up from sitting position
Low femoral neck BMD*	Dementia
History of fractures*	Poor calcium intake
Corticosteroid use*	Low BMI*
Cigarette smoking*	Limited exercise
Alcohol intake >2 U/d*	Caffeine intake
Asian and white races	
Recurrent Falls	

*Risk factors included in the WHO model.

Alendronate has also been found to be beneficial in men: 241 men with osteoporosis were studied in a 2-year, double-blind, placebo-controlled trial. The men who received alendronate had a mean increase in BMD of 7.1% at the LS, 2.5% at the femoral neck, and 2.0% for the total body. Vertebral-fracture incidence was lower in the treated versus the placebo group (0.8% vs. 7.1%), and height loss was significantly greater in the placebo than in the alendronate group (2.4 vs. 6 mm) [19].

The efficacy of alendronate on glucocorticoid induced osteoporosis (GIO) has been established. A 2-year trial of 477 men and women taking glucocorticoids showed significant increases in mean LS BMD by 2.1% and 2.9%, respectively, with 5 and 10 mg of alendronate per day. The femoral neck bone density significantly increased by 1.2% and 1.0% in the respective alendronate groups [20].

A head-to-head study comparing weekly alendronate, 70 mg, with risedronate, 35 mg, for 1 year revealed small but significantly greater increases in BMD at 6 and 12 months and greater degrees of bone suppression in the alendronate group, with similar tolerability [21]. This study was not powered to detect differences in fracture rates.

Risedronate

This drug is available in a 5-mg once-daily, a 35-mg weekly, and a 150-mg monthly dose. A delayed-release formulation, Atelvia, 35-mg weekly dose was recently approved by the FDA. Risedronate is FDA approved for prevention and treatment of postmenopausal osteoporosis, prevention and treatment of GIO, and treatment of osteoporosis in men.

Two large randomized, placebo-controlled studies showed a reduction in radiographic vertebral fractures by 41% to 49% after 3 years with risedronate [22,23]. One of these trials was extended to 7 years. This follow-up revealed persistence of

Table 4.6. Recommendations for Osteoporosis Screening

Women age 65 y or older and men age 70 and older
All adults with a history of fragility fractures
Postmenopausal women younger than 65 y but with clinical risk factors for fractures
Men and women with known secondary causes of osteoporosis (long-term glucocorticoid therapy, primary hyperparathyroidism)

BMD gains and fracture relative risks(RRs) through the 7th year of follow-up [24]. In the largest trial conducted, with hip fracture as the primary end point, risedronate significantly reduced the risk of these fractures by 30% [25]. In the subgroup of patients with known osteoporosis, a significant 40% RR for fracture was seen.

A meta-analysis on the use of risedronate for postmenopausal osteoporosis showed a pooled RR of 0.64 for vertebral and 0.73 for nonvertebral fractures [26]. The pooled estimates of the differences in percentage of change between risedronate (5 mg) and placebo were 4.54% at the LS and 2.75% at the femoral neck.

Postmenopausal women who were treated with risedronate for 3 years were followed for 1 year after discontinuation of risedronate. During the year off treatment, BMD of LS and femoral neck declined but remained significantly higher compared to baseline BMD and the placebo group BMD. Urinary NTX and BSAP levels had declined significantly, while on risedronate, however, 1 year after discontinuation of risedronate, the levels were not significantly different from placebo. But despite the above changes, the risk of new morphometric vertebral fractures was 46% lower in the former risedronate group compared to the control group [27].

The efficacy of once-weekly risedronate was shown in a randomized, placebo-controlled study of 1,456 postmenopausal women with *T*-scores less than 2.5 or less than 2.0 with a prevalent vertebral fracture taking 5-mg daily, 35-mg weekly, or 50-mg weekly doses. Mean percentage changes in LS BMD after 12 months were similar, as were mean increases in femoral neck BMD in the three groups [28].

Risedronate 150-mg once a month oral dose was shown to be noninferior compared to the 5-mg daily regimen administered to postmenopausal women with osteoporosis with regard to changes in hip BMD and changes in BTMs. There was no difference in the incidence of adverse events between the two groups [29].

Risedronate is also effective in prevention and treatment of glucocorticoid-GIO, as evidenced by two major prospective studies [30,31].

Ibandronate

Ibandronate is available in two oral forms, 2.5 mg daily and 150 mg monthly, as well as an intravenous (IV) form, 3 mg quarterly. Ibandronate is FDA approved for prevention and treatment of postmenopausal osteoporosis.

The Monthly Oral Pilot Study was a randomized, double-blind, multicenter, placebo-controlled study of 144 postmenopausal women who were given 50, 100, or 150 mg of ibandronate or placebo. No significant differences in adverse events compared with placebo were observed. Ibandronate also significantly decreased serum CTXs in those taking 100- or 150-mg dosages [32]. The MOBILE study was a 2-year, randomized, double-blind trial that evaluated the appropriate ibandronate dose for the treatment of osteoporosis. The 1,609 women in the study were assigned to four groups of ibandronate: 2.5 mg daily, 50 mg/50 mg (single doses on consecutive days) monthly, 100 mg once a month, or 150 mg once a month. The LS BMD increased by 3.9%, 4.3%, 4.1%, and 4.9%, respectively, in the above groups. The 150-mg group had a small but significantly greater increase in LS BMD than did those on the daily regimen. In addition, when the groups were evaluated for those who achieved BMD gains above baseline as well as more than 6% at the LS or 3% at the hip, the 150-mg and 100-mg groups had significantly more patients at these goals compared to the daily regimen. Regarding side effects, the frequency of gastrointestinal symptoms with each dose was similar, but a small increase in flu-like symptoms was noted with the monthly regimens [33]. During the MOBILE Long-Term Extension (LTE) study, patients continued monthly ibandronate for 3 years. After 5 years of treatment with ibandronate (100 and 150 mg dosing), the LS BMD increased by 8.2% and 8.4% and femoral neck BMD increased by 2.4% and 3.2%, respectively, compared to MOBILE baseline [34].

The Dosing IntraVenous Administration (DIVA) study was a randomized, double-blind, double-dummy, noninferiority study of 1,395 women with osteoporosis receiving IV ibandronate (2 mg every 2 months or 3 mg every 3 months) or daily oral ibandronate (2.5 mg). The lumbar BMD gains were higher in the 2- and 3-monthly IV regimens compared to oral dosing (6.4%, 6.3%, and 4.8%, respectively, $p < 0.001$). The reduction in C-telopeptide of the alpha chain of type 1 collagen was similar in all groups. Tolerability profile was similar for all regimens [35]. A 3-year extension of the DIVA study (DIVA LTE) showed that patients receiving 5 years of treatment showed an increase in LS BMD of 8.4% (2 mg every 2 months) and 8.1% (3 mg every 3 months) compared with DIVA baseline.

In a randomized, double-blind, placebo-controlled, parallel-group study, 2,946 postmenopausal women with BMD *T*-score less than or equal to −2.0 at the LS and history of vertebral fracture received either placebo or ibandronate 2.5 mg/d or 20 mg every other day for 12 doses every 3 months. At the end of the 3-year study period, there was a 6.5%, 5.7%, and 1.3% increase in LS BMD in the daily ibandronate, intermittent ibandronate, and placebo groups, respectively. The risk of new morphometric vertebral fractures was reduced by 62% ($p = 0.0001$) and 50% ($p = 0.0006$) in the daily and intermittent ibandronate groups, respectively, compared to placebo. There was a 49% and 48% relative RR in clinical vertebral fractures in the daily and intermittent ibandronate groups, respectively. The incidence of nonvertebral fractures was similar between the groups. However, in post hoc analysis, there was a significant reduction in risk of nonvertebral fractures in the patients with femoral neck *T*-score less than −3.0 receiving daily ibandronate (69%, $p = 0.012$) [36].

Zoledronic Acid

Zoledronic acid is FDA approved for the prevention and treatment of postmenopausal osteoporosis, treatment of GIO, and treatment of osteoporosis in men. It is administered as a 5-mg (Reclast) IV infusion over 15 minutes once yearly. The 4-mg monthly dosing (Zometa) is used for treatment of skeletal complications of malignancy.

The Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) trial was a multicenter, randomized, double-blind, placebo-controlled study of 7,765 patients that compared the effects of annual infusions of zoledronic acid over 3 years to placebo. Treatment with zoledronic acid reduced risk of morphometric vertebral fracture by 70% during the study period compared to placebo and reduced risk of hip fracture by 41%. The risk of nonvertebral fractures, clinical fractures, and clinical vertebral fractures were reduced by 25%, 33%, and 77%, respectively. LS BMD increased by 6.71% and femoral neck BMD increased by 5.06% in the zoledronic acid group compared to placebo ($p < 0.001$). At 12 months, the levels of serum C-telopeptide of type 1 collagen, BSAP, and N-terminal propeptide of type 1 collagen were significantly lower (59%, 30%, and 58%, respectively) in the zoledronic acid group compared to placebo. The levels of bone markers were similar at 6 and 12 months after each infusion [37].

In a randomized, double-blind, placebo-controlled trial of patients who received either yearly zoledronic acid or placebo within 90 days of surgical repair of hip fracture, there was a 35% RR for any new clinical fracture in the zoledronic acid group. The rates of new clinical vertebral fractures and new nonvertebral fractures were also lower in the zoledronic acid group. There was a 28% reduction in all-cause mortality in the zoledronic acid group [38].

Safety Concerns

Esophagitis

Bisphosphonates are alkaline substances that have been reported to cause esophageal and gastric ulcers. An initial Mayo Clinic study reported esophagitis among alendronate-treated patients [39]. This is the reason that patients are advised to remain upright after taking the bisphosphonates. Which oral bisphosphonate is more erosive remains controversial. Head-to-head endoscopy studies have shown conflicting results [40,41]. A meta-analysis of eight trials that included 10,086 patients showed no difference in gastrointestinal adverse events, clinically or endoscopically, in patients treated with risedronate versus placebo [42].

Osteonecrosis of the Jaw

There have been recent reports of patients who have suffered from osteonecrosis of the jaw (ONJ) while on bisphosphonates therapy. The exact pathogenesis is not clear, but having recent dental work appeared to be a risk factor. The vast majority of the patients were on IV bisphosphonates (monthly zoledronic acid and every 3 months pamidronate for cancer indications), and only a small proportion of patients were on alendronate and risedronate for osteoporosis [43]. A study examining the incidence of ONJ in the HORIZON trial found that the incidence of ONJ was similar in the zoledronic acid and placebo groups (one patient from each group experienced ONJ) [44]. Overall, the incidence of ONJ remains low in the noncancer population treated with bisphosphonates.

Atrial Fibrillation

In the HORIZON trial (3 years of annual zoledronic acid infusions compared to placebo), there was a higher occurrence of atrial fibrillation in the zoledronic acid group compared to placebo (50 vs. 20 patients, $p < 0.001$) [37].

This finding prompted further evaluation of a possible link between use of bisphosphonates and atrial fibrillation. The results of the FIT trial were reviewed, 1.5% of the patients in the alendronate group were diagnosed with serious atrial fibrillation (defined as events resulting in hospitalization or disability or judged to be life threatening) compared to 1.0% of the placebo group, but the difference was not statistically significant ($p = 0.07$). There was no increased risk of all atrial fibrillation adverse events (2.5% vs. 2.2%).

The information was reviewed by the FDA including data from over 19,000 bisphosphonate-treated patients and greater than 18,000 placebo-treated patients who were followed for 6 months to 3 years. In a statement issued by the FDA in 2008, it was concluded that the occurrence of atrial fibrillation was rare and there was no clear association between overall bisphosphonate exposure and the rate of atrial fibrillation (serious or nonserious). The FDA is monitoring postmarket reports of atrial fibrillation. A population-based case-control study using medical databases from Denmark found no evidence of bisphosphonate use and increased risk of atrial fibrillation [45].

Atypical Femoral Fractures

There has been concern about atypical femoral fractures in association with bisphosphonate use. The American Society for Bone and Mineral Research (ASBMR) task force issued a statement [4] regarding atypical subtrochanteric and diaphyseal fractures (see Table 4.7). Based on review of the available data while a causal relationship between the use of bisphosphonates and atypical fractures has not been established, it was postulated that bisphosphonates can potentially contribute to factors increasing risk of these fractures. These include reduced angiogenesis, alteration in collagen cross-linking and maturation, increased advanced glycation

end products, reduced heterogeneity of bone mineralization, bone remodeling, and microdamage accumulation. This report [4] included data from the Study of Osteoporotic Fractures (SOF), which was a prospective population-based US study of 9,704 Caucasian women over the age of 65, which showed an overall incidence of subtrochanteric fractures to be 3 per 10,000 patient-years (compared to 103 cases per 10,000 patient-years for overall incidence of hip fractures). Older age, lower total hip BMD, and history of falls were identified as predictors of subtrochanteric fractures; however, after multivariate analysis, only age remained a significant factor.

The task force also reviewed data from a large US Health Maintenance Organization (HMO), which included 15,000 total hip and femur fractures in women over the age of 45. Data from 600 possible atypical fractures were examined, 102 had features consistent with atypical fracture, and 97/102 patients had been treated with bisphosphonates. Preliminary estimates showed a progressive increase in risk of atypical fracture from 2 per 10,000 cases per year to 78 per 10,000 cases per year with 2 and 8 years of bisphosphonate treatment, respectively. While the incidence of atypical fractures was low and there was no control group to compare to, there was an increased risk of atypical femoral fractures with longer duration of bisphosphonate treatment.

Based on case reports and case series, 310 cases have been reported with 286 occurring in patients treated with bisphosphonates for osteoporosis and five patients treated for malignancy; there was no bisphosphonate use in the remaining cases. The duration of bisphosphonate therapy ranged from 1.3 to 17 years with mean duration of 7 years. Glucocorticoid use was identified in 76 of the cases. Other risk factors noted in some series have included proton pump inhibitors (PPI) use, comorbid conditions (i.e., RA or diabetes mellitus [DM]), age younger than 65 (which is in contrast to the SOF data), and vitamin D deficiency.

There is limited histologic data available in patients with atypical femoral fractures with majority of the data obtained from iliac crest biopsies and a small number of biopsies performed at or near the subtrochanteric fracture region. However, it is important to keep in mind that the biopsy results from the site of the fracture can be affected by the changes occurring in response to the fracture. In general, the biopsies have revealed low bone turnover and lack of double tetracycline labeling (in some cases, single label was present).

The results of bone markers have not been consistent. In many cases, the BTMs were not suppressed to the extent that would be anticipated based on biopsy results, but it is important to keep in mind that the markers may have been affected by the fracture itself. More data from biopsy results obtained from patients on bisphosphonate treatment with and without atypical femoral neck fractures as well as data regarding BTMs are necessary to shed light on changes present that set atypical fractures apart from other types of fractures.

Based on available data, the incidence of atypical femoral neck fractures is very low and the risk benefit profile favors using bisphosphonates for fracture prevention. However, it is important to note that the incidence of atypical femoral fractures may be underestimated secondary to lack of awareness and underreporting. It has been recommended to establish an international registry of patients with atypical fractures and conduct further research to identify the clinical and genetic risk factors that lead to higher risk of developing atypical femoral fractures [46].

A secondary analysis of the FIT, FLEX, and HORIZON trials reviewed the incidence of subtrochanteric and diaphyseal femur fractures. In this study, femoral neck, subcapital, periprosthetic, pathologic, and high-energy fractures were excluded. Overall, this study identified 12 atypical fractures, a combined rate of 2.3 per 10,000 patients. The data showed that the risk of atypical fracture associated

Table 4.7. Atypical Femoral Fracture: Major and Minor Features

Major Features*
Located anywhere along the femur from just distal to the lesser trochanter to just proximal to the supracondylar flare
Associated with no trauma or minimal trauma, as in a fall from standing height or less
Transverse or short oblique configuration
Noncomminuted
Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex
Minor Features
Localized periosteal reaction of the lateral cortex
Generalized increase in cortical thickness of the diaphysis
Prodromal symptoms such as dull or aching pain in the groin or thigh
Bilateral fractures and symptoms
Delayed healing
Comorbid conditions (e.g., vitamin D deficiency, RA, hypophosphatasia)
Use of pharmaceutical agents (e.g., bisphosphonates, glucocorticoids and proton pump inhibitors)

Note: femoral neck, intertrochanteric fractures with spiral subtrochanteric extension, pathologic fractures associated with primary or metastatic tumors, and periprosthetic fractures were excluded.

*All major features need to be present to qualify as an atypical femoral fracture, but none of the minor features are required.

with bisphosphonate use is very low. The relative hazard (RH) ratio compared to placebo was 1.03 (95% CI, 0.06–16.46) for the FIT (alendronate) trial, 1.33 (95% CI, 0.12–14.67) for the FLEX trial (continuation of FIT), and 1.5% (95% CI, 0.25–9.00) for the HORIZON (zoledronic acid) trial. It is important to note several limitations of this study including lack of radiographic information to assess the atypical features of the fractures, the small number of events (therefore low statistical power), exclusion of patients treated with confounding medications by design, and lack of long-term data [47].

It is not clear which patients are at higher risk of atypical fractures with bisphosphonate use, but case reports have suggested that longer duration of bisphosphonate treatment (however, the reported ranges of bisphosphonate treatment has been between 1.3 and 17 years, with median duration of 7 years) and the concomitant use of corticosteroids, PPIs, and other antiresorptive treatments may be associated with higher risk of atypical fractures.

To evaluate fractures, conventional radiographs (anteroposterior and lateral views) can be sufficient. In equivocal cases or in patients with normal radiographic findings but high suspicion for an evolving fracture technetium bone scan, MRI or spiral CT may be helpful. For patients with atypical fracture, bisphosphonate treatment should be stopped. Orthopedic evaluation may be necessary. In case reports, teriparatide has shown promise in fracture healing and can be a consideration for treatment [46].

The optimal duration of bisphosphonate treatment is not clear. The duration of treatment should be based on history of fractures, fracture risk, and BMD. Markers of bone turnover may aid in decision-making as well. Treatment with bisphosphonates for 5 years appears to be safe and provide antifracture benefit.

In the FLEX trial, there was a lower risk of clinical vertebral fracture in patients who remained on alendronate for 10 years compared to those who stopped alendronate after 5 years [17]. Based on the risedronate data, treatment for 7 years did not lead to further fracture reduction compared to 3 and 5 years of treatment [24]. According to the 2010 AACE guidelines, it is reasonable to give a "drug holiday" after 4 to 5 years of bisphosphonate therapy for patients with low or moderate risk of fracture and 10 years for high-risk patients [48]. For high-risk patients, alternative agents, such as teriparatide, could be used during the drug holiday.

This is an evolving area that needs more data; specifically, it is not clear if a drug holiday will decrease the risk of atypical femoral fractures and the optimal duration of the drug discontinuation period. After discontinuing bisphosphonates, it is important to closely monitor clinical status, bone markers, and BMD. Resuming treatment can be considered if there is a fracture or a significant decline in BMD.

Esophageal Cancer

The FDA recently reviewed all the publications on esophageal cancer and concluded that the data linking oral bisphosphonates to esophageal cancer are inconclusive. (http://www.fda.gov/Drugs/DrugSafety/ucm263320.htm)

Raloxifene

Raloxifene (Evista) is a selective estrogen receptor modulator, with agonistic effects on bone. The major efficacy trial for raloxifene was the Multiple Outcomes of Raloxifene Evaluation (MORE) trial [49]. The LS BMD increase over the 3-year study period was 2% to 3%, and vertebral fracture–reduction rates in women with and without preexisting fractures were 50% and 30%, respectively. No significant difference in nonvertebral and hip fracture reduction was observed. Efficacy of raloxifene was sustained through 4 years of treatment [50]. A meta-analysis of seven trials comparing raloxifene and placebo showed a similar BMD increase at the LS and a 2% increase for the combined hips [51].

The Continuing Outcomes Relevant to Evista (CORE) trial was a 4-year extension of the MORE trial. The placebo-treated group continued with placebo, and those previously treated with raloxifene (60 or 120 mg/d) received raloxifene 60 mg/d. The secondary end point of the study was new nonvertebral fractures. The risk of at least one new nonvertebral fracture was similar in the placebo (22.9%) and raloxifene (22.8%) groups, with an HR of 1.00 (Bonferroni-adjusted CI, 0.82, 1.21). Based on a subgroup analysis, 7 years after MORE randomization, the difference in the LS and femoral neck BMD with raloxifene were 1.7% ($p = 0.30$) and 2.4% ($p = 0.045$), respectively, compared to placebo. Compared to MORE baseline, 7 years of raloxifene treatment significantly increased LS (4.3% from baseline, 2.2% from placebo) and femoral neck BMD (1.9% from baseline, 3.0% from placebo). At all time points, femoral neck and spine BMD were significantly higher in the raloxifene group compared to MORE baseline. Some limitations of this study included differences in the populations studied. The women who enrolled in CORE were younger and had less severe osteoporosis compared to those who did not enroll. The placebo group had fewer prevalent fractures at MORE baseline compared to the raloxifene group. Of note, since CORE's primary end point was cancer prevention, bone-active agents were permitted after the 3rd year of MORE study and a significantly higher percentage of women in the placebo group used bone-active treatment compared to the raloxifene group. Approximately 20% of CORE participants did not take the study drug. These differences may have affected the ability to detect a difference in fracture incidence between the groups. Also, BMD was assessed in a subgroup of patients and therefore may not have been representative of the entire group [52].

This drug has other potential benefits, including reduction in breast cancer risk and improvement in lipids and markers of cardiovascular (CV) disease, but these are not discussed in this section.

Calcitonin

Because of its modest effect on BMD, its fracture reduction, and its systemic analgesic effects, this drug is useful as an alternative agent after an acute vertebral fracture. However, the authors believe that it should be used with a stronger antiresorptive when possible. The major efficacy trial was the Prevent the Recurrence of Osteoporotic Fractures (PROOF) study, which demonstrated a 1.2% increase in LS BMD and a 33% reduction in vertebral fractures with 200 IU of intranasal calcitonin [53]. No significant reduction was seen in the 100- or 400-IU groups. No significant reduction in nonvertebral and hip fractures was demonstrated in this trial. In a meta-analysis of 30 trials that compared calcitonin with placebo, the smaller studies were found to have more impressive results than the PROOF study [54]; the authors of that meta-analysis suggested a possible bias in the smaller studies.

Hormone Replacement Therapy

Hormone replacement therapy (HRT) was the initial antiresorptive therapy for osteoporosis. However, current controversies centered on increased breast cancer and CV risks have resulted in a marked decline in use for osteoporosis. A meta-analysis of 57 randomized studies that compared at least 1 year of HRT in postmenopausal women with controls showed a trend toward reduction of vertebral and nonvertebral fracture incidence. BMD increased by 6.76% at 2 years in the LS and 4.12% in the femoral neck [55]. Perhaps the best prospective data to date that showed fracture reduction with combined HRT were those established in the Women's Health Initiative study. The incidence of clinical vertebral fractures was reduced by 34%, hip fractures by 34%, and all fractures by 24%. However, increased breast cancer and CV risk led to discontinuation of this treatment arm. Absolute excess risks per 10,000 person-years attributable to estrogen plus progestin were eight more coronary heart disease events, eight more strokes, eight more pulmonary emboli, and eight more invasive breast cancers, whereas absolute RRs per 10,000 person-years were six fewer colorectal cancers and five fewer hip fractures [56].

Combination Therapy

Combined HRT and alendronate have demonstrated superiority in BMD benefit over either agent alone. In a 2-year study of 425 postmenopausal women who were randomly assigned to receive estrogen, alendronate, a combination of the two, or placebo, the mean change in LS BMD was statistically higher with combination therapy than with either agent alone [57]. Another trial gave alendronate,10 mg/d, or placebo to 428 postmenopausal women receiving HRT for at least 1 year. After 12 months, alendronate produced significantly greater BMD increases in the LS (3.6% vs. 1.0%) and the hip trochanter (2.7% vs. 0.5%) than did placebo [58].

A study comparing raloxifene, 60 mg/d, and alendronate, 10 mg/d, in combination or alone, in 331 postmenopausal women with femoral neck *T*-scores less than −2 found a significantly greater LS BMD increase in the combination group than in those with alendronate or raloxifene alone (3.7% vs. 2.7% vs. 1.7%, respectively) [59].

Teriparatide (PTH 1-34)

Synthetic human PTH 1-34, or teriparatide (Forteo), is an anabolic agent that has been approved for treatment of postmenopausal and male osteoporosis. The landmark trial in postmenopausal women was the Fracture Prevention Trial (FPT). In this study, 1,637 postmenopausal women received placebo, 20 or 40 μg daily

subcutaneous injections of teriparatide for a mean of 21 months. In the groups treated with teriparatide, vertebral fractures decreased by 65% and 69%, respectively, and nonvertebral fractures were reduced by 53% and 54%. Mean increases in LS BMD of 9% and 13%, as well as 3% and 6% at the femoral neck, were seen. The most common side effects were nausea and headaches [60].

Teriparatide is approved for only 2 years of use; therefore, it is of interest to see what happens to the bone mass of patients who discontinue the drug. Extensions of the FPT have looked at changes in BMD and fracture risk after discontinuation of teriparatide. One study found that 30 months after discontinuation of teriparatide, the hazard ratio for nonvertebral fragility fractures was still significantly lower than with placebo but only in the 40-μg group. BMD decreased over those months in both groups, except in those who received bisphosphonates for at least 2 years during the trial [61]. Another study looked at vertebral BMD changes and fractures 1.5 years after discontinuing teriparatide. There continued to be a statistically significant increase in BMD and a decrease in fractures in those who had been taking teriparatide. Those who used bisphosphonates for at least 1 year continued to gain BMD, whereas those who did not lost BMD [62].

A randomized study of 93 postmenopausal women with low BMD examined the effects of alendronate 10 mg/d, teriparatide 40 mg/d, or both over 30 months. The LS BMD increased more in the group treated with teriparatide compared to alendronate or the combination group. A similar pattern was observed for femoral neck BMD. Bone markers increased more in the teriparatide group compared to the alendronate or combination group. The results showed that alendronate reduced the anabolic effect of teriparatide [63].

A randomized, double-blind trial compared teriparatide, 40 μg, with alendronate, 10 mg daily. By 3 months, and through the 14 months of the study, those in the teriparatide group experienced significantly greater increases in LS and hip BMD than with alendronate. The incidence of nonvertebral fractures was significantly lower in the teriparatide group compared to the alendronate group [64].

The effects of teriparatide after administration of alendronate or raloxifene have been assessed. During the first 6 months, the prior raloxifene group had higher gains in BMD at the LS and the hip whereas the prior alendronate group did not. After the first 6 months, the rates of increase were similar in both groups. At 18 months, the raloxifene group had gained 10.2% in LS BMD, compared with 4.1% in the alendronate group ($p < 0.001$) [65].

Teriparatide also has been shown to increase bone mass by 13% in the LS and 2.9% in the femoral neck in men with idiopathic osteoporosis [66]. A randomized trial of 83 men, with LS or femoral neck *T*-score of at least −2, compared teriparatide, alendronate, and their combination over a 2.5-year period (teriparatide was started at month 6). The teriparatide group had significant increases in LS BMD and femoral neck BMD, which were greater than those in the alendronate and combination groups [67]. In a study that assessed BMD and fractures for 30 months after a year of exposure to teriparatide, LS and total hip BMD remained significantly higher in the PTH group than in the placebo group, even though the BMDs decreased after discontinuation. When the subjects were divided according to bisphosphonate use, those who took bisphosphonates had an increase in spine and hip BMD, although significant intergroup differences were lost. Among those who did not take bisphosphonates, the BMD decreased. A significant decrease in moderate to severe spine fractures was seen at 18 months of follow-up [68].

The frequency of transient hypercalcemia within 4 to 6 hours after administration is 10-fold higher among patients who received teriparatide compared with placebo, and in one-third of these, the transient hypercalcemia was reverified on consecutive measurements. The occurrence of leg cramps was also significantly higher in the

teriparatide group compared to the placebo group [60]. The drug carries a black box warning for osteosarcoma in rats. Teriparatide caused a dose- and duration-dependent increase in this condition among rats treated with the drug. For this reason, children, patients with prior radiation therapy, and those with high bone turnover, such as bone metastasis or Paget disease of bone, should not receive the drug.

In a large clinical trial involving 1,637 postmenopausal women, antibodies to PTH (1-34) developed in 1 woman in the placebo group (<1%), 15 women in the 20 μg/d group (3%), and 44 women in the 40 μg/d group (8%). The antibodies did not have an effect on any of the parameters measured [60].

Studies examining continuous versus cyclic PTH treatment for osteoporosis have been promising. In one study, 126 women with osteoporosis who were treated with alendronate for at least 1 year were assigned to receive daily subcutaneous PTH (25 μg) or cycles of 3 months of daily PTH followed by 3 months without PTH, or alendronate 70 mg alone for 15 months. There was no significant change in biochemical markers of bone turnover in the alendronate group. In the groups who received PTH, the markers of bone formation increased during the periods when PTH was administered. Bone-resorption markers increased in both PTH groups but more so in the daily-treatment group than in the cyclic-therapy group. The BMD of LS significantly increased by 6.1% in the group who received the daily PTH and 5.4% in the cyclic-therapy group compared to the alendronate group. The difference in LS BMD gains was not significant between the PTH groups. The hip BMD increased marginally in all groups with no significant difference between the groups. The study was not statistically powered to detect a difference in fracture outcomes. The study showed that cyclical administration of PTH resulted in the dissociation of the early anabolic phase of PTH from the subsequent bone remodeling phase allowing for a greater anabolic effect and therefore achieving similar changes in BMD with administration of 60% of the PTH in the cyclic administration group compared to the daily administration group [69]. Women from this study who were treated with teriparatide and remained at high risk for fracture (17 from the original daily teriparatide group and 15 from the cyclical teriparatide group) were enrolled in a follow-up study after 1 year of alendronate alone to receive a second course of teriparatide (daily) for 15 months while remaining on alendronate. The mean spine BMD increased by 4.7% in the prior daily teriparatide group and by 4.9% in the prior cyclical teriparatide group after retreatment [70].

While teriparatide is an effective treatment for osteoporosis, its mode of administration can be a limiting factor for some patients. A randomized, placebo-controlled phase 2 study examined the safety and efficacy of transdermal teriparatide patch (doses 20, 30, or 40 μg, worn for 30 min/d) compared to placebo patch and subcutaneous administration of 20 μg/d of teriparatide in 165 postmenopausal women with osteoporosis. Over a 6-month period, the LS BMD increased in all teriparatide patch groups in a dose-dependent manner compared to placebo. At 6 months, mean percentage (SD) change from baseline LS BMD was 2.96%, 3.47%, and 4.97% in the 20-, 30-, and 40-μg transdermal teriparatide groups, respectively. There was a 3.55% increase in LS BMD in the subcutaneous teriparatide group. The BMD change in LS in the group who received the 40 μg/d teriparatide patch was comparable to the BMD increase in the group who received daily subcutaneous teriparatide injections. All groups showed a significant improvement in LS BMD compared with the placebo group. There was a 1.33% increase in total hip BMD in the 40 μg/d teriparatide patch group compared to a 0.09% change in total hip BMD in the subcutaneous teriparatide group at 6 months. The reason for this finding is unclear. The patch showed a higher peak concentration and a shorter half-life compared to

subcutaneously injected teriparatide. Whether the pharmacokinetics of subcutaneous teriparatide resulted in the difference between the two groups is not clear, and further studies are necessary to explore this finding. The change in femoral neck BMD was not statistically significant after 6 months in the treatment groups. BTMs (procollagen type 1 N-terminal propeptide and C-terminal cross-linked telopeptide of type 1 collagen) significantly increased from baseline values in a dose-dependent manner in all teriparatide patch treatment groups compared to placebo patch. The transdermal patch was well tolerated, and there was no significant difference between the adverse events in the transdermal and subcutaneous teriparatide groups. During the 6 months of therapy, no clinically significant hypercalcemia was observed. Additional studies are necessary to further evaluate the efficacy and safety of transdermal teriparatide over a more extended period of time [71].

Safety Concerns

Teriparatide was approved by the FDA in December of 2002. It carries a "black box" warning for potential increased risk of osteosarcoma, which was observed in high percentage of rodents treated with high doses of teriparatide for most of their lifespan.

The first case of suspected osteosarcoma was reported in 2005 in a postmenopausal female in her 70s with osteoporosis that was diagnosed with metastatic cancer during her 2nd year of treatment with teriparatide. The patient subsequently died, no autopsy was performed, and the primary site of tumor was not identified, but based on bone pathology data, she was diagnosed with osteosarcoma.

A second case was reported in 2010 of a 67-year-old male with history of recurrent prostate cancer. The patient was treated with proton therapy 7 years prior to diagnosis of osteosarcoma of the left pubic ramus. The diagnosis was made after 2 months of treatment with teriparatide. The authors felt that the radiation exposure was the main contributor given the latency period between the time of radiation exposure and diagnosis of osteosarcoma, the occurrence of the tumor within the radiation field, as well as the short time period between teriparatide exposure and diagnosis, which is in conflict with the timeline of tumorigenesis observed in animal studies. However, it is not clear if teriparatide enhanced the development of osteosarcoma in this case. A postmarketing surveillance program for evaluation of an association between osteosarcoma and treatment with teriparatide is ongoing and is expected to continue through 2013 [72].

Denosumab

Receptor activator of nuclear factor κB ligand (RANKL) binds to its receptor RANK on osteoclasts and osteoclast precursors acting as a key mediator of osteoclast differentiation, action, and survival. This process is regulated by a decoy receptor called OPG that binds RANKL and prevents activation of osteoclasts. Denosumab is a human monoclonal antibody to RANKL that reversibly inhibits osteoclast-mediated bone resorption. Denosumab is FDA approved for the treatment of osteoporosis in postmenopausal women and is administered as a 60-mg subcutaneous injection every 6 months.

In a 2-year randomized, double-blind, placebo-controlled phase 3 study, 332 postmenopausal women with LS *T*-scores between −1.0 and −2.5 were assigned to receive either denosumab (60 mg subcutaneously every 6 months) or placebo. The primary end point was change in LS BMD at 24 months. In the denosumab group, the LS BMD increased by 6.5% compared to a 0.6% decline in the placebo group. The total hip, femoral neck, and distal one-third radius BMD were

significantly higher in the denosumab group compared to placebo at 24 months. There was a significant reduction in bone-resorption markers at 1 month and throughout the study in the denosumab group compared to placebo. There was a gradual decline in P1NP, a marker of bone formation, in the denosumab group, which was sustained through the end of the study. There was a transient decrease in serum calcium level compared to baseline after the first dose of denosumab, which subsequently normalized and remained stable thereafter. The overall incidence of adverse events was similar between the two groups; however, there was a higher percentage of patients who reported infection (sore throat) and rash in the denosumab group [73].

In the randomized, placebo-controlled Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM trial), 7,868 women with *T*-scores between −2.5 and −4.0 at the LS or total hip were assigned to receive either 60 mg of denosumab or placebo subcutaneously every 6 months for 36 months. The primary end point of the study was new vertebral fracture. There was a 68% relative RR of developing new vertebral fracture (2.3% in the denosumab group and 7.2% in the placebo group), a 40% relative RR of developing hip fracture, and a 20% relative RR in developing nonvertebral fracture compared to placebo. After 36 months, LS BMD increased by 9.2% and total hip BMD increased by 6.0% in the denosumab group compared to placebo. Denosumab decreased serum CTX by 86% at 1 month and by 72% at 6 and 32 months. P1NP levels were also lower compared to the placebo group. There was no significant difference in adverse effects between the groups. There were no cases of ONJ [74].

The Study of Transitioning from Alendronate to Denosumab (STAND) trial was a phase 3 multicenter, randomized, double-blind study; 504 postmenopausal women with a BMD *T*-score between −2.0 and −4.0 on alendronate therapy for at least 6 months were assigned to either continue alendronate therapy or receive denosumab 60 mg subcutaneous every 6 months for a period of 12 months. The primary end point was the percent change in total hip BMD. In the denosumab group, total hip BMD increased by 1.90% compared to a 1.05% increase in the alendronate group. The LS, femoral neck, and distal one-third radius BMD were also significantly higher in the denosumab group compared to the alendronate group. Serum CTX levels were significantly lower in the denosumab group compared to the alendronate group. The safety profile was similar in both groups [75].

A phase 3, double-blind, multicenter trial compared the efficacy and safety of denosumab (60 mg subcutaneously every 6 months) with alendronate (70 mg weekly) in postmenopausal women with *T*-score less than or equal to −2.0 at total hip or LS. Denosumab significantly increased total hip BMD by 3.5% compared to 2.6% in the alendronate ($p < 0.0001$) group after 12 months of treatment. A similar pattern was seen at the femoral neck, LS, and distal one-third radius BMD. Serum CTX was significantly lower in the denosumab group until 12 months at which point the decrease in CTX was similar in both groups. P1NP level was significantly lower in the denosumab group throughout the study and at 12 months. The study was not powered to compare fracture rates between the two groups. The overall safety profile was similar for both groups [76].

Denosumab has also been studied in women with breast cancer treated with adjuvant aromatase inhibitor (AI) therapy. Women with LS, total hip, or femoral neck *T*-score between −1.0 and −2.5 on AI (≤6 months or >6 months of treatment) were randomized to receive denosumab or placebo. At 12 and 24 months, the LS BMD significantly increased by 5.5% and 7.6%, respectively, in the denosumab group compared to placebo. The increase in BMD was not influenced by

theduration of AI treatment. The study was not powered to assess treatment effect on fracture rate [77].

While denosumab is not FDA approved for use in men, a study of men on androgen deprivation therapy for prostate cancer treated with denosumab or placebo for 24 months showed a significant increase in LS, femoral neck, and distal one-third radius BMD compared to placebo. There was also a significant decrease in the incidence of new vertebral fractures (1.5% in the denosumab group vs. 3.9% in the placebo group) [78].

In the absence of head-to-head trials, it is not possible to compare fracture prevention efficacy of denosumab to other treatments for osteoporosis. Some of the advantages of denosumab include improved patient compliance compared to weekly or monthly oral bisphosphonates, lack of long-term skeletal accumulation, and the ability to use denosumab in patients with renal impairment.

Calcium and Vitamin D Supplementation

In a meta-analysis of 15 trials comparing calcium with placebo, the pooled increase in percentage change from baseline was 2.05% for the total body BMD, 1.66% for the LS, and 1.64% for the hip in patients who received calcium. Vertebral fracture risk decreased by 23% and nonvertebral fracture risk by 14% in the calcium group [79].

The recommended intake of elemental calcium is 1,000 to 1,200 mg/d for adults older than 50 years. Intake more than 2,000 to 2,500 mg is not recommended, as it may cause hypercalciuria (see section on calcium in "Hypocalcemia"). Vitamin D supplementation has been found to reduce vertebral fractures by 37% in a meta-analysis of 25 trials. A trend was noted toward reduction in nonvertebral fractures as well (RR, 0.72; $p = 0.09$). Patients who received hydroxylated forms of vitamin D had larger increases in BMD than did those who received vitamin D_2 [80]. According to the Institute of Medicine (IOM), the Recommended Dietary Allowance (RDA) for vitamin D is 600 IU daily between the ages of 9 and 70 and 800 IU for people over age 70. The NOF recommends 800 to 1,000 IU of vitamin D a day. The AACE recommends between 1,000 to 2,000 IU of vitamin D a day. Patients with history of malabsorption or bariatric surgery will need higher doses of vitamin D to achieve the desired level. Most experts agree that a minimal level of 30 ng/dl of vitamin D up to 50 to 60 ng/dl is an acceptable target range (also refer to Section on Vitamin D Deficiency).

A recent meta-analysis examined the effect of calcium supplements on the risk of CV events. Eligible studies were randomized, placebo-controlled trials of calcium supplements (≥500 mg/d) and study duration of more than 1 year. The researchers found 143 people allocated to calcium had a myocardial infarction compared with 111 allocated to placebo (hazard ratio 1.31, 95% CI 1.02–1.67, $p = 0.035$). While there was a higher incidence of stroke, when the composite end point of myocardial infarction, stroke, or sudden death was examined, the difference did not reach statistical significance. The meta-analysis of trial level data showed similar results. It is important to note that CV end points were not the primary outcomes for these studies, and the studies did not include patients on calcium and vitamin D. Further data are necessary to further evaluate the above findings [81].

In response to this article, ASBMR issued a statement that numerous large studies of calcium with vitamin D have not shown an increased risk of CV events. It was recommended that patients discuss calcium intake with their health care professional as calcium and vitamin D are important for bone health. It was noted that elderly individuals and those with renal impairment who are on calcium supplementation may be at higher risk of CV complications. The U.S. FDA has begun a safety analysis on calcium supplements.

Other Therapies

The use of hip protectors may reduce hip fractures in those at high risk; however, adherence is only about 40% [82]. Weight-bearing and back-strengthening exercises are also helpful adjunctive measures in the management of osteoporosis.

Future Therapies

Strontium Ranelate

Strontium ranelate is an oral agent that has been shown to increase bone formation and decrease bone resorption. It has emerged as a possible new therapy for osteoporosis. It is approved in Europe for treatment of osteoporosis, but it is not approved in the United States.

In the Spinal Osteoporosis Therapeutic Intervention (SOTI) phase 3 clinical trial, there was a 41% relative RR in development of new vertebral fractures in postmenopausal women with osteoporosis treated with 2 g of oral strontium compared to placebo over 3 years. There was a 14.4% and 8.3% increase in LS and femoral neck BMD, respectively, in the strontium group compared to placebo. The most common gastrointestinal side effect was diarrhea, but this abated after 3 months.

In the Treatment of Peripheral Osteoporosis study (TROPOS), there was a 16% relative RR for development of nonvertebral fractures in postmenopausal women with osteoporosis who were treated with strontium for 3 years compared to placebo [83].

In a 3-year open-label extension study of women who had participated in the SOTI and TROPOS trials, the cumulative incidence of any osteoporotic fracture was not significantly different compared to the first 3 years in the SOTI and TROPOS trials. There was a significant increase in BMD of LS, femoral neck, and total hip throughout the study with the exception of the 8-year BMD for the femoral neck and total hip [84].

PTHrP

PTH-related protein (PTHrP) that is associated with humoral hypercalcemia of malignancy has many similar properties as PTH since it binds to PTH-1 receptors. In animal models, administration of PTHrP has been shown to increase BMD. In a small, double-blind, prospective, placebo-controlled, randomized clinical trial of 16 postmenopausal women with osteoporosis, the group who received 400 μg/d of subcutaneously administered PTHrP over 3 months had a 4.7% increase in LS BMD compared to placebo. There was no significant difference between the two groups with regard to femoral neck BMD. In the PTHrP group, there was an increase in serum osteocalcin; however, there was no significant difference in other BTMs (including BSAP) between the two groups. Whether the same bone turnover pattern will hold true for longer period of PTHrP administration is not clear. There was no change in the serum total or ionized calcium levels. Further clinical trials are necessary to evaluate this drug for treatment of osteoporosis [85].

Wnt/β-Catenin Signaling Pathway

Binding of Wnt to frizzled receptors and to low-density lipoprotein receptor–related protein (LRP) 5 and 6 coreceptor results in gene transcription leading to osteoblastic cell differentiation and bone formation. This pathway is being studied for new therapeutic approaches for treatment of osteoporosis. Sclerostin is a product of SOST gene that binds LRP5/6 and inhibits the Wnt signaling pathway. Mutations of this gene cause sclerosteosis and van Buchem disease characterized by increased bone mass. Inactivation or antagonization of sclerostin can lead to increased bone mass, and this has been shown in animal studies using humanized monoclonal antibodies to sclerostin.

In a randomized, double-blind, placebo-controlled phase 1 study, sclerostin monoclonal antibody was administered to healthy men and postmenopausal women who were followed for 85 days. Dose-related increases in bone-formation markers were observed along with dose-related decreases in bone-resorption markers. There was a statistically significant increase in BMD of up to 5.3% at the LS and 2.8% at the total hip in the treatment group compared to placebo [86].

Clinical phase 2 studies examining the efficacy of sclerostin antibody are currently under way. While the effects of Wnt activation on bone have been favorable, there is concern about tumorigenicity in nonskeletal sites and more studies are necessary to evaluate the safety profile of this therapeutic approach [87].

SERM

Currently, the only FDA-approved SERM is raloxifene. However, there are newer SERMs in development with the aim of providing greater fracture reduction in addition to reduction or prevention of breast carcinoma development. The Postmenopausal Evaluation and Risk-Reduction with Lasofoxifene trial examined the effects of lasofoxifene on the risk of fractures, estrogen receptor (ER)–positive breast cancer, and CV disease in 8,556 postmenopausal women with osteoporosis. Patients received once daily lasofoxifene (0.25-mg or 0.5-mg dose) or placebo for a period of 5 years. Lasofoxifene (0.5 mg) was associated with a lower incidence of vertebral fractures, nonvertebral fractures (not seen with raloxifene), ER-positive breast cancer, and major coronary heart disease events. The results were less consistent for the lower lasofoxifene dose. The incidence of venous thromboembolic events was higher for both doses of lasofoxifene [88].

Tibolone

Tibolone is a synthetic steroid with estrogenic, progestogenic, and antiandrogen properties. It is used for treatment of postmenopausal symptoms and osteoporosis prevention in other countries, but it is not FDA approved in the United States. The Long-Term Intervention on Fractures with Tibolone (LIFT) trial was a randomized, double-blind, placebo-controlled study examining the effect of 1.25 mg of tibolone daily on the risk of fractures over 3 years in 4,538 postmenopausal women with osteoporosis. Tibolone decreased risk of vertebral fracture by 45% and decreased risk of nonvertebral fracture by 26%. The tibolone group also had a lower incidence of invasive breast cancer and colon cancer but a higher incidence of stroke. Treatment with tibolone was also associated with gynecologic symptoms (vaginal bleeding and discharge) as well as breast discomfort [89].

Cathepsin K Inhibitors

CTSK is a cysteine protease expressed in osteoclasts that degrades type 1 collagen. Loss-of-function mutation in the gene encoding CTSK causes pycnodysostosis, a rare disease characterized by osteosclerosis, short stature, and bone fragility. Odanacatib has been shown to selectively and reversibly inhibit CTSK, therefore decreasing bone resorption in phase 1 studies. A 1-year dose-finding trial with a 1-year extension on the same treatment dose was performed in postmenopausal women with low BMD (T-scores of ≤ -2.0 but > -3.5 at the LS or femoral sites) to evaluate the safety and efficacy of odanacatib. Patients received odanacatib (doses 3, 10, 25, or 50 mg weekly) or placebo for 24 months. The primary end point was percentage change in LS BMD from baseline. The 50-mg dose of odanacatib increased LS BMD by 5.5% and total hip BMD by 3.2%, respectively, compared to placebo. The safety and tolerability of odanacatib were similar to placebo [90]. A 1-year extension study showed that continued treatment with 50 mg of odanacatib for 3 years produced significant increases from baseline and from year 2 in spine BMD (7.9% and 2.3%) and total hip BMD (5.8% and 2.4%) [91]. It is being tested in phase 3 trials for its fracture

reduction efficacy. Other CTSK inhibitors are currently being studied, and the role that they may play in the treatment of osteoporosis is not yet clear.

Src Kinase Inhibitors

Src kinase is a key enzyme in regulation of osteoclast-mediated bone resorption. Src kinase inhibitors are being studied for treatment of osteoporosis and cancer-related bone disease.

Monitoring Therapy

Most experts would agree that DXA scans should be obtained 1 to 2 years after initiation of treatment until bone stability has been demonstrated. Therapy should not be changed if BMD decline is seen after 1 year of treatment, because it has been found that some patients who "lose" bone after 1 year tend to gain bone later. This was demonstrated in a post hoc analysis of data from the FIT and the MORE trials. In examining the baseline, 1-year, and 2-year BMDs of the patients in these studies, the investigators found that the degree of BMD decline the 1st year on treatment was associated with a gain in BMD the next year. This phenomenon is known as "regression to the mean"; that is, outlying results may be due to random or technical error that may not represent true biologic change, and subsequently, these changes revert to the mean. If loss continues in succeeding DXAs, therapy can be altered at that time [92]. Furthermore, one study showed significant fracture protection while taking bisphosphonate therapy, even among patients who lost up to 4% in the spine or the hip [93].

BTMs are helpful in determining efficacy of therapy and patient compliance. The most commonly used bone-resorption markers include urinary NTX and serum CTX. Markers of bone formation often used include BSAP and serum osteocalcin (see earlier Section on Evaluation of Metabolic Bone Disorders). Fracture protection being the primary end point, it is important for clinicians to monitor patients for the occurrence of new fractures. Repeated fractures while receiving therapy may warrant a change in therapy or reevaluation for secondary causes of osteoporosis. The majority of vertebral compression fractures are asymptomatic, however. A study that assessed the correlation between height loss and vertebral fractures found that height loss of greater than 2 cm in 3 years had the sensitivity for new vertebral fractures of only 36% but a specificity of almost 94%. The positive predictive value for this degree of height loss was about 35%, and the negative predictive value was about 92% [94]. Thus, height measurement should be accurately performed during patient visits.

In addition to initiating treatment for osteoporosis and assessing response to therapy, it is also important to evaluate patients for a "drug holiday." In the past, many patients were treated with bisphosphonates for many years and some indefinitely; however, the newer approach is to take patients off treatment when the clinical scenario is appropriate. Based on the most recent AACE guidelines, patients treated with alendronate for 4 to 5 years can be considered for a 1- to 2-year drug holiday. High-risk patients could receive longer therapy prior to stopping bisphosphonates, and use of teriparatide should be considered during the holiday. The decision to resume therapy will depend on the patient's fracture risk. When bone loss ensues or the patient fractures, therapy should be resumed. Low-risk patients with low bone mass or osteopenia can have relatively longer "drug holidays."

PAGET DISEASE OF BONE

Paget disease is a metabolic bone disorder resulting from exaggerated osteoclastic bone resorption and formation of architecturally disrupted and weak bone. This causes skeletal pain, deformity, and fractures.

Epidemiology

The estimated prevalence, based on autopsies and review of radiographs, is about 3%. The disease is commonly seen in Britain, Australia, New Zealand, and the United States. Rare in people younger than 20 years, it is most commonly diagnosed at age 50 years.

Pathophysiology

The exact etiology of Paget disease is currently unknown. Family history of the disease is identified in 12% to 23% of patients, and environmental factors, such as measles, exposure to lead, and previous dog ownership, have been linked to the disease.

The primary disturbance seems to be increased activation of the osteoclasts. Large, multinucleated osteoclasts can be seen in the borders of the lesion that apposes normal bone.

Diagnosis

Most affected patients have no symptoms, so diagnosis is based on serendipitous findings of a high alkaline phosphatase (ALP) or abnormal radiographs. Some patients, however, have symptoms, or they may have already had complications at the time of diagnosis. Common complaints include dull, achy bone pain and various bony deformities, such as enlargement of the skull or bowing of the long bones. Fractures, arthritis in the nearby joints, hearing loss, nerve impingement, high-output heart failure, and osteosarcoma are complications of Paget disease.

Biochemically, an elevated total or BSAP suggests the presence of the disease. Serum and urine calcium levels are rarely elevated unless the patient becomes immobilized. Markers of bone resorption such as urinary CTX and NTX and osteocalcin values are usually high.

Pagetic areas are visualized as areas of intense uptake on bone scan. Usually, the whole bone is involved, such as in the pelvis, vertebrae, or scapula. A leading edge shaped like a flame or the letter V may be seen in the appendicular bones. Plain radiographs of the affected areas will show cortical thickening and irregular areas of lucency and sclerosis. Pagetic involvement of the skull usually shows enlargement due to cortical thickening and areas of sclerosis and lucencies giving an appearance of cotton-wool. Bowing deformities of the long bones, particularly the tibia, may be appreciated.

Treatment

Treatment is targeted toward slowing osteoclastic bone resorption. Indications are outlined in Table 4.8. Oral and IV bisphosphonates are the most commonly used agents for treatment of Paget disease, particularly risedronate, alendronate, zoledronic acid, and less commonly pamidronate.

Bisphosphonates

Risedronate

The recommended dose is 30 mg/d for 2 months, with an optional 3rd month if no decline in ALP is seen 1 month after the end of treatment. In an open-label study of 162 patients, 30 mg of risedronate was given for 84 days, followed by 112 days without therapy. The cycle was repeated if the ALP remained high or increased by 25%. Normalization of ALP was seen in 54% of patients after 7 to 14 months of therapy. A significant decrease in bone pain also occurred [95].

A randomized, controlled trial comparing risedronate (30 mg/d for 60 days) with etidronate (400 mg/d for 6 months) showed better efficacy with risedronate than etidronate. At 12 months, ALP normalized in 73% of risedronate-treated

Table 4.8. Indications for Treatment of Paget Disease

Serum ALP ≥ 3 or 4 times upper limit of normal
Fractures or pain in involved bone
Involvement of critical sites that may lead to complications such as arthritis or fractures or nerve compression
Skull involvement associated with hearing loss or headache
Monostotic disease of weight-bearing bones
Pretreating patients before surgery to reduce hypervascularity and blood loss

patients, compared with only 15% in the etidronate group. This value also normalized faster in the risedronate group (3 months vs. 1 year) [96].

Alendronate

Alendronate is administered at 40 mg/d, typically for 6 months. In a double-blind, randomized, placebo-controlled study of 55 patients, 40 mg/d of alendronate resulted in normalization of ALP in 48% of patients. Declines in urine NTX and ALP were seen in 86% and 73% of patients, respectively. Radiographic improvement was noted in 48% of patients [97].

A head-to-head trial of alendronate (40 mg/d) and etidronate (400 mg/d), both administered for 6 months, showed higher rates of normalization of ALP (61% vs. 17%) and greater reduction in ALP (79% vs. 44%), with alendronate than with etidronate. No evidence of osteomalacia was seen on bone biopsies of patients in the alendronate group, whereas one patient taking etidronate was found to have osteomalacia, a known complication of large doses of this drug [98].

Zoledronic Acid

Zoledronic acid is FDA approved for treatment of Paget disease. The recommended dose is 5 mg IV over 15 minutes. In two randomized, double-blind, active-controlled trials, patients were given either one dose of 5 mg of zoledronic acid or 30 mg of risedronate for 2 months. After 6 months, more subjects taking zoledronic acid experienced a disease response (96% vs. 74%), ALP normalized more often in the zoledronic acid group (89% vs. 58%), the quality of life in those who received zoledronic acid was higher, and fewer patients in the zoledronic acid group had a relapse [99].

In a 15-month randomized study, 120 patients with Paget disease received either pamidronate (30 mg IV for 2 consecutive days every 3 months) or zoledronic acid (single 4 mg IV dose). At 6 months, zoledronic acid was associated with higher rate of ALP normalization (93% vs. 35% compared to pamidronate). The nonresponders to pamidronate were crossed over to zoledronic acid or neridronate (100 mg IV for 2 consecutive days) with 94% and 93% therapeutic response (defined as normalization of AP or 75% reduction in total AP), respectively. Zoledronic acid was superior with respect to pamidronate in achieving biochemical remission, with therapeutic response maintained in most patients at 15 months [100]. The biochemical remission can last up to 2 years [101].

Pamidronate

IV pamidronate is ideal for patients who are unable to tolerate oral bisphosphonates. It also may be used as a therapeutic trial in those who have pain of indeterminate nature in an area involved with Paget disease. Dosing is determined by disease severity. The recommended dose is a 30-mg IV infusion over a 4-hour

period (in 500 ml saline or 5% dextrose) for 3 consecutive days. However, most clinicians opt for higher doses such as 60 or 90 mg given once, followed by ALP monitoring. Biochemical remissions are usually sustained for 12 to 18 months, depending on disease severity.

A prospective, nonrandomized study of 80 patients with Paget disease investigated the use of 180 mg IV over a 3- or 6-week period. ALP declined by 63% compared with baseline, and 62% achieved normalization of ALP [102].

Common side effects include flu-like symptoms or mild fever for a few days after the infusion and, more rarely, iritis.

Calcitonin

Calcitonin is available as salmon or human preparations for subcutaneous administration. Calcitonin nasal spray has not been approved for this disease. The starting dose for the subcutaneous injection is 100 Medical Research Council (MRC) of salmon calcitonin at bedtime. After clinical improvement, which can generally be expected in a few weeks to months, the dose can be reduced to half every other day.

Other Therapies

Nonsteroidal anti-inflammatory agents and analgesics play supportive roles in the management of Paget disease. Patients who need fracture repairs, joint replacements, and osteotomies for severe bowing deformities are usually comanaged with orthopedic surgeons. Neurosurgeons may be involved when evidence of compressive neurologic damage is present.

PRIMARY HYPERPARATHYROIDISM

Primary hyperparathyroidism (PHPT) is classically known as a disease of "stones, bones, abdominal moans, and groans with psychic overtones." With the advent of autoanalyzers in the mid-1970s and early detection of hypercalcemia, asymptomatic hyperparathyroidism has become more common, and it currently accounts for up to 80% of cases encountered by clinicians. More recently, due to more widespread screening for parathyroid disease in patients with osteoporosis, a new form of normocalcemic hyperparathyroidism has also been described.

Epidemiology

Primary hyperparathyroidism (PHPT) occurs in 2 to 3 per 1,000 women and in 1 per 1,000 men in the United States. It usually occurs among people in their sixth or seventh decade. Ten percent of hyperparathyroidism is familial, inherited in an autosomal dominant manner in syndromes such as familial hyperparathyroidism, multiple endocrine neoplasia (MEN) 1 and 2A, and hyperparathyroidism–jaw tumor syndrome. Onset of hyperparathyroidism is usually earlier among patients with these inherited syndromes [103].

Pathogenesis

PHPT arises from proliferation of parathyroid cells that have a decreased calcium-sensing ability. Potential etiologies include genetic alterations, such as cyclin D1/parathyroid adenomatosis 1 (*CCND1/PRAD-1*), *MEN1*, and other gene mutations, and radiation exposure. In addition, prolonged calcium or vitamin D deficiency may lead to parathyroid cell proliferation due to downregulation of the calcium-sensing receptors on parathyroid cells [103]. Thiazide diuretics may exaggerate or unmask the hypercalcemia in many cases.

PHPT is due to parathyroid adenomas in 80%, parathyroid hyperplasia in 15%, a "double adenoma" in 1% to 2%, and parathyroid carcinoma in 1% of cases. In the hands of an experienced surgeon, parathyroid adenomas can be successfully identified and resected in more than 90% of cases. However, ectopic adenomas may be seen in unusual locations such as in the tracheoesophageal groove, the

carotid bifurcation, or the thymus. Hyperplasia of multiple glands is more common in those with familial or MEN syndromes.

Clinical Presentation

PHPT may present with nephrolithiasis (most common manifestation); neurologic symptoms such as confusion, difficulty concentrating, depression, dementia, and fatigue; CV abnormalities such as hypertension, left ventricular hypertrophy, valvular calcifications, QT prolongation, and arrhythmias; gastrointestinal manifestations such as anorexia, nausea, vomiting, abdominal pain, constipation, pancreatitis, and peptic ulcer disease; other renal abnormalities such as renal insufficiency, polyuria, polydipsia, and nephrocalcinosis; and musculoskeletal manifestations such as osteopenia, osteoporosis, osteitis fibrosa cystica, proximal muscle weakness, gout, pseudogout, bone or joint pains, and chondrocalcinosis [103]. It is important to remember that most patients are asymptomatic; however, even in asymptomatic patients, a higher risk of CV disease and mortality, as well as subtle nonspecific neuropsychiatric manifestations, has been reported [104].

Diagnosis

Because most patients have asymptomatic hyperparathyroidism, the history and physical examination rarely clinch the diagnosis. They are considered in ruling out other causes of hypercalcemia. A family history of hypercalcemia should be sought, and a careful review of the patient's medication list should be undertaken.

Biochemical features include hypercalcemia and a high or inappropriately normal intact PTH. Urinary calcium excretion is high in fewer than 50% of cases, but it is usually greater than 200 mg/24 hr. The urine calcium/creatinine ratio is usually more than 0.01. The challenge arises in patients with normocalcemia and mild elevations of intact PTH. In these cases, 25-hydroxyvitamin D and creatinine levels should be checked to rule out secondary hyperparathyroidism. Once secondary causes have been carefully excluded, those patients can be diagnosed with normocalcemic PHPT. On long-term follow-up of these patients, hypercalcemia, albeit mild, eventually manifests. In one study, 40% of patients with this entity developed manifestations of PHPT after 3 years of follow-up [105]. Phosphate levels are typically in the low-normal range; they are frankly low in fewer than 25% of cases.

The classic radiologic findings in advanced disease are nephrolithiasis, subperiosteal bone resorption, thinning of the distal third of the clavicle, and osteitis fibrosa cystica (Table 4.9).

Lithium and thiazide use can mimic PHPT, occurring with mild hypercalcemia and elevated intact PTH levels. If it is clinically safe, these drugs should be discontinued and reevaluation performed in 2 to 3 months.

Initial evaluation should include a DXA scan of the spine and hip. If available, distal radius bone density should be done as well. The radius area, composed primarily of cortical bone, is affected to a greater degree by PHPT. Serum creatinine should be obtained, and a renal ultrasound performed to screen for nephrolithiasis and nephrocalcinosis. Familial benign hypocalciuric hypercalcemia (FBHH), which typically occurs with asymptomatic hypercalcemia, is usually associated with a 24-hour urinary calcium excretion of less than 100 mg and a fractional excretion of calcium less than 0.01.

Vitamin D deficiency is found in more than half of patients with PHPT, and vitamin D status should be routinely assessed in these patients. There is evidence that correcting vitamin D deficiency does not exacerbate hypercalcemia, and may result in lowering PTH levels and BTMs. Urinary calcium should be monitored closely in these patients as vitamin D replacement may cause or worsen hypercalciuria [106].

Treatment

Surgical Management

Surgery by an experienced endocrine surgeon is the definitive treatment. Patients with symptomatic disease, including those who have had an episode of life-threatening hypercalcemia, should be treated surgically. The Third International Workshop on the Management of Asymptomatic PHPT in 2008 recommended these guidelines for surgery in patients who have asymptomatic disease [107]:

- Serum calcium level higher than 1 mg/dl above the upper limit of normal
- *T*-score less than −2.5 at the LS, total hip, femoral neck, or distal radius and/or previous fragility fracture
- Age younger than 50 years
- Calculated creatinine clearance less than 60 ml/min
- Patients for whom medical surveillance is not desirable or possible

Urinary calcium excretion more than 400 mg/24 hr is not one of the Third Workshop's criteria for parathyroid surgery but is still considered as such by several experts [107].

Patients without clear indications for surgical intervention can be monitored with annual serum calcium and creatinine checks and bone density evaluation every 1 to 2 years [107]. Surgical referral can be considered in these patients as well, since surgery is the only known curative therapy for PHPT and many asymptomatic patients who initially have no surgical indications eventually develop complications or meet criteria for surgery. In a 10-year prospective cohort study of 121 patients with asymptomatic PHPT, 61 patients underwent parathyroidectomy and 60 patients were observed without surgery, as they had remained asymptomatic with no evidence for complications of the disease. All patients who underwent parathyroidectomy had normalization of their serum calcium concentrations and improvement in their LS and femoral neck

Table 4.9. Clinical Manifestations of PHPT

Musculoskeletal	**Cardiovascular**
Osteoporosis	Hypertension
Fractures	Left ventricular hypertrophy
Muscle weakness and fatigue	Valvular calcifications
	Increased vascular stiffness
Renal	
Nephrolithiasis	**Rheumatologic**
Renal insufficiency	Gout
Mild hypomagnesemia	Chondrocalcinosis
Hypophosphatemia	Pseudogout
Neuropsychiatric	**Hematologic**
Anxiety	Normochromic, normocytic anemia
Depression	
Cognitive dysfunction	**Ocular**
	Band keratopathy

BMD by 8% and 6%, respectively, at 1 year, and 12% and 14%, respectively, at 10 years. No changes were observed in serum calcium concentrations, urinary calcium excretions, or BMDs in those who did not undergo surgery. In 14 of those patients who initially did not undergo surgery, disease progression developed, requiring parathyroidectomy [108]. In another observational study of 116 patients with PHPT who did not undergo surgery and were followed for 15 years, BMD started worsening at the 9th year of follow-up, and about 60% of patients had significant bone loss by the end of the observation period [109].

Minimally invasive surgery requires the use of preoperative localization studies. These include ^{99m}Tc sestamibi scan, which has a good sensitivity and can localize ectopic parathyroid adenomas; neck ultrasound, which is safe and inexpensive but is highly operator dependent; and CT or MRI, which are usually used when other modalities are nonlocalizing or after failed surgery. In cases of failed primary surgery and negative imaging, invasive techniques such as arteriography and selective venous sampling with PTH measurement may be necessary, but these should be done by highly experienced individuals. In addition to preoperative localization, intraoperative PTH monitoring can increase surgical success rates for PHPT. In the hands of an experienced surgeon, parathyroidectomy is a safe, cost-effective procedure with minimal complications and a success rate of up to 95% [110].

Medical Management

In patients with mild, uncomplicated PHPT, many will need no therapy at all. Scholz et al. showed that in roughly 25% of such patients, a need for operation developed within 10 years [111]. Two other groups (Henry Ford Hospital and Columbia University) reported similar results [108,112]. Individuals who meet criteria for surgery but are not surgical candidates or who refuse surgery should be treated medically. Patients are advised about maintaining adequate hydration and avoidance of thiazide diuretics. Moderate oral calcium intake (750–1,000 mg/d) also is advised.

Bisphosphonates may be useful agents in patients with PHPT. Several studies have examined the effect of alendronate on BMD, serum calcium, PTH, and BTMs in patients with PHPT. Treatment with alendronate was consistently associated with an increase in BMD and decrease in bone-resorption markers. Effects on serum calcium and serum PTH levels were variable but transient in the majority of cases [113–117]. In a recent meta-analysis comparing bisphosphonate therapy to surgical intervention and to no intervention in patients with mild PHPT, bisphosphonates resulted in a similar increase in bone density compared to parathyroidectomy, whereas patients with no intervention had a small but significant degree of bone loss [118].

Estrogen therapy in this disease has been associated with mild declines in serum calcium levels and increases in BMD. The risks of estrogen therapy for this purpose must be carefully discussed with patients.

The newest therapeutic agent for this disease is the calcimimetic cinacalcet. This drug acts on calcium-sensing receptors on parathyroid cells to reduce PTH production directly. Cinacalcet was shown to normalize serum calcium in patients with PHPT after the second dose when compared with placebo, and this effect was maintained for the duration of therapy and accompanied by a decrease in PTH levels [119]. In a subsequent multicenter, randomized, double-blind, placebo-controlled trial, cinacalcet 30 mg twice daily (titrated to 40 mg then 50 mg twice daily at 4 and 8 weeks if hypercalcemia persisted) reduced serum calcium by at least 0.5 mg/dl in 73% of patients with mild PHPT compared to placebo, along with decreasing PTH levels. The mean calcium levels in the treatment group decreased to normal within 2 weeks of therapy initiation. No changes in BMD were noted

in cinacalcet-treated patients, but there was an increase in BTMs in this group [120]. In a 4.5-year open-label extension of the same study where all patients were treated with cinacalcet, placebo patients achieved a similar reduction in their calcium levels compared to the original cinacalcet group, and their serum calcium normalized within 1 month after cinacalcet initiation. All subjects subsequently maintained a normal serum calcium throughout study duration. PTH levels also showed a sustained decrease throughout the study duration but did not normalize. Serum ALP increased with cinacalcet treatment and remained elevated but within the normal reference range. There was no significant change in BMD after cinacalcet treatment, but there was a trend toward increased *Z*-scores [121]. In an open-label, single-arm trial, cinacalcet was given to patients with persistent PHPT after surgical intervention or patients with PHPT who were not surgical candidates. Cinacalcet reduced serum calcium in 88% of these patients, but PTH levels were highly variable in this study, and no clear PTH reduction was seen. There was no significant change in BTMs, and BMD was not reported [122]. A pooled analysis of data from the three above trials confirmed the effectiveness of cinacalcet in reducing calcium and PTH levels regardless of disease severity [123]. In 2011, this drug became FDA approved for treatment of severe hypercalcemia in patients with PHPT who are unable to undergo parathyroidectomy [124].

PARATHYROID CARCINOMA

Epidemiology

This disease is a rare entity of the parathyroid glands. It is seen in fewer than 1% of cases of PHPT. Parathyroid carcinoma usually presents at a younger age compared to benign PHPT, typically in the mid-40s, and it affects men and women equally, with no gender preference [125].

Pathogenesis

The pathogenesis of parathyroid carcinoma is still unclear. There is strong evidence linking this cancer to mutations in the HRPT2 gene, which may be found in 15% to 100% of cases of sporadic parathyroid carcinoma. Mutations of the cyclin D1/parathyroid adenomatosis gene 1 (PRAD1), retinoblastoma (Rb), p53, and breast carcinoma susceptibility (BRCA2) genes may play a role as well. Parathyroid carcinoma has also been linked to other diseases and conditions, such as renal failure, neck radiation, and hereditary disorders of the parathyroid glands such as hereditary hyperparathyroidism–jaw tumor syndrome, familial isolated hyperparathyroidism, and MEN types 1 and 2A. Hyperparathyroidism–jaw tumor syndrome, an autosomal dominant condition that involves a mutation in the HRPT2 gene, is associated with a higher chance of developing parathyroid carcinoma [125,126].

Clinical Manifestations

The majority of patients with parathyroid carcinoma present with symptoms and signs of hypercalcemia. Around 50% to 75% of patients with parathyroid carcinoma will have a palpable neck mass. Symptoms due to local invasion are rare and may include hoarseness due to damage to the recurrent laryngeal nerve [125,126].

Biochemically, patients with parathyroid carcinoma are found to have markedly elevated calcium (at least 14 mg/dl) and PTH (up to 10 times normal) levels. Elevated ALP levels may be found as well [125,126].

Patients with parathyroid carcinoma are more likely to develop renal and skeletal complications of hyperparathyroidism compared to patients with benign PHPT. The proportion with renal stones or insufficiency can range from approximately 32% to 84%, compared to fewer than 20% in patients with benign PHPT. Skeletal manifestations including osteitis fibrosa cystica, absent lamina dura, subperiosteal

bone resorption, and decreased BMD have been reported in 44% to 91% of these patients, compared to less than 10% in patients with benign disease [125,126].

Diagnosis

Clinical and biochemical features that raise suspicion for parathyroid carcinoma include male sex, younger age, a palpable neck mass, markedly elevated serum calcium and/or PTH levels, and advanced renal or bone disease. Nuclear scans may aid in the localization of the abnormal gland. Ultrasound can help assess the features of the abnormal parathyroid gland; a higher length/width ratio, lobulation, and heterogeneous echotexture are features that have been associated with parathyroid carcinoma. However, definitive diagnosis is made based on histologic criteria and vascular and capsular invasion [125,126].

Treatment

The mainstay of treatment is resection of the primary tumor and of recurrence. This carcinoma often recurs at the resection site and via contiguous spread. Recurrence occurs in over 50% of patients, usually about 2 to 3 years after resection. Metastases occur later by way of the lymphatic and hematologic spread. When the carcinoma does spread, the lungs and the cervical nodes are affected more often and the liver is involved in about 10% of cases. The 5-year survival rate can range from 40% to 86% [125,126].

Given the likelihood of recurrence, such other treatments as radiation and chemotherapy have been investigated, with limited results. Several options are available to control the hypercalcemia that can ensue with unresectable disease. IV bisphosphonate infusions can reduce the calcium concentration. Calcitonin is less effective. The calcimimetic agent cinacalcet was shown to significantly reduce serum calcium levels in patients with inoperable parathyroid carcinoma and is currently approved for this use [127,128].

HYPERCALCEMIA

The most common causes of hypercalcemia are PHPT and malignancy. Together, they account for about 90% of cases. Other causes of serum calcium elevation are outlined in Table 4.10. Most patients with PHPT are asymptomatic, whereas those with malignancies and hypercalcemia usually have advanced and readily apparent disease. Signs and symptoms of hypercalcemia are reviewed in Table 4.11.

Diagnosis

With the advent of routine biochemical screening, hypercalcemia is detected earlier, and most patients are asymptomatic or have few clinical symptoms. It is prudent to repeat the serum calcium test or confirm hypercalcemia with measurement of an ionized calcium level before embarking on an expensive workup. Because the most common cause is PHPT, the first step is to obtain an intact PTH to determine whether the hypercalcemia is mediated by PTH.

PHPT usually is initially seen with mild to moderate hypercalcemia (usually <11 mg/dl) and high or inappropriately normal PTH values. Serum phosphate values may be normal or low, and 24-hour urinary calcium excretion may be normal or high. Mild hyperchloremia can be seen.

Rapid onset of hypercalcemia points to humoral hypercalcemia of malignancy. PTHrP levels are elevated in 60% to 80% of cases.

If hypercalcemia is not mediated by PTH or PTHrP, 25(OH)D and $1,25(OH)_2D$ should be measured. If elevated, the first step is to rule out exogenous intake. Granulomatous diseases or lymphomas cause hypercalcemia by increasing 1α-hydroxylation of 25(OH)D. Phosphate levels and urinary calcium excretion may be normal or high.

Familial hypocalciuric hypercalcemia (FBHH) is first seen with hypercalcemia and low urinary calcium excretion. The fractional excretion of calcium is usually less than 0.01. Family history of hypercalcemia should be elicited [180].

Intact PTH is usually suppressed in hypercalcemia due to hyperthyroidism, milk-alkali syndrome, immobilization experienced by patients with Paget disease, vitamin A and D toxicities, and rarely adrenal insufficiency.

Treatment

Address the Primary Cause

Surgery is the treatment of choice for PHPT, if the patient meets criteria. In hypercalcemia of malignancy, treatment should be directed at the primary malignancy after it has been identified. Medications likely contributing to the hypercalcemia should be discontinued, and the patient retested in 2 to 3 months. No treatment is required for FBHH.

Decrease Intestinal Absorption

In chronic granulomatous diseases or lymphoma, glucocorticoids, such as prednisone, 20 to 40 mg/d, effectively reduce calcium levels. Of note, higher doses may be required for lymphoma. Although rarely used, antimalarial agents such as chloroquine and hydroxychloroquine reduce endogenous calcitriol production, and they may be used as well. Exogenous calcium, vitamin D, and oxalate intake should be limited.

Oral phosphates (250–500 mg four times daily) may be used to limit intestinal calcium absorption by forming calcium phosphate complexes. However, when the calcium–phosphorus product is too high, ectopic calcifications may result.

Increase Urinary Calcium Excretion

Hydration is the most important first step. This can be achieved through infusion of IV 0.9% NaCl, which increases delivery of calcium to the loop of Henle. The rate of saline infusion must be adjusted in patients with congestive heart failure or renal insufficiency. Electrolytes should be carefully monitored and replaced. If normocalcemia is not achieved, patients may be carefully given diuretics, such

Table 4.10. Common Causes of Hypercalcemia

Increased Bone Resorption	***Downregulation of Parathyroid Calcium-Sensing Receptor***
Primary hyperparathyroidism	Familial hypocalciuric hypercalcemia
Malignancy: PTHrP, ectopic PTH production, cytokine production, osteolytic bone metastasis	Lithium
Hyperthyroidism	***Decreased Renal Excretion of Calcium***
Vitamin A intoxication	Thiazide diuretics
Paget disease with immobilization	Acute renal failure
Increased Intestinal Calcium Absorption or Exogenous Administration	***Others***
Vitamin D intoxication	Adrenal insufficiency
Granulomatous and lymphoproliferative diseases	
Milk-alkali syndrome	
Hemodialysis	
Hyperalimentation	

Table 4.11. Clinical Manifestations of Hypercalcemia

Gastrointestinal	***Cardiovascular***
Constipation	Shortened QT interval
Anorexia	Calcium deposition in coronary arteries, myocardium, and heart valves
Abdominal pain	Hypertension
Peptic ulcer due to increased gastrin production	***Musculoskeletal***
Renal	Muscle weakness
Nephrolithiasis, nephrocalcinosis	Chondrocalcinosis
Renal insufficiency	***Others***
Nephrogenic diabetes insipidus	Band keratopathy, limbic calcification
Renal tubular acidosis	
Neuropsychiatric	
Depression, anxiety, decreased cognitive function	
Psychosis, hallucination, lethargy, coma with higher calcium levels	

as furosemide, to facilitate calcium excretion. This must be done only once the patient is fluid replete.

Inhibit Bone Resorption

Bisphosphonates

IV bisphosphonates are effective in reducing serum calcium values. The effect is not achieved until a few days after administration, but it is more sustained than with IV hydration, furosemide, or calcitonin.

Zoledronic acid is approved for the treatment of hypercalcemia of malignancy. It is a third-generation bisphosphonate that is 100 to 800 times more potent than pamidronate. In a randomized, double-blind study of 287 patients with hypercalcemia of malignancy, zoledronic acid (4 and 8 mg) or pamidronate (90 mg) were given to patients with serum calcium levels exceeding 12 mg/dl. Both doses of zoledronic acid were superior to pamidronate, with response rates by day 10 of 88.4% (4 mg zoledronic acid), 86.7% (8 mg zoledonic acid), and 69.7% (90 mg pamidronate) for zoledronic acid, 4 and 8 mg, and pamidronate, 90 mg, respectively. Normalization of serum calcium by day 4 was approximately 45% to 55% in the zoledronic acid groups and only 33.3% in the pamidronate-treated patients [129].

Pamidronate was widely used before the introduction of zoledronic acid. The recommended dose depends on the severity of hypercalcemia, ranging from 30 to 90 mg infused over a 2- to 4-hour period. A study comparing pamidronate with clodronate in 41 patients with hypercalcemia of malignancy had more favorable results for pamidronate than in this trial. In this investigation, pamidronate normalized calcium levels in all patients by a median of 4 days and the normocalcemia lasted for 28 days [130]. The optimal frequency of pamidronate administration can be variable. One small, prospective, randomized trial found that infusion of pamidronate every 2 weeks conferred less hypercalcemia than that every 3 weeks (10% vs. 50%) [131]. Given that bisphosphonates are excreted by the kidneys, dosage should be adjusted in cases of renal insufficiency.

Calcitonin
The dose of calcitonin is 4 IU/kg intramuscularly or subcutaneously every 12 hours. This dose works rapidly, reducing calcium levels by 1 to 2 mg/dl over that achieved with hydration only; however, tachyphylaxis is frequently seen after 2 or 3 days. Thus, the drug is a useful adjunct while waiting for the IV bisphosphonate to take effect.

Mithramycin
This drug is given intravenously at a dose of 25 mg/kg over a 3- to 6-hour period. Serum calcium decreases within 12 hours, and this effect lasts for several days. However, a small, randomized, prospective study in patients with hypercalcemia of malignancy demonstrated serum calcium normalization in only 3 of the 11 patients taking mithramycin [132]. Contraindications to the drug include liver, kidney, or bone marrow disease. Because of numerous hematologic side effects and the effectiveness of previously described drugs, it is infrequently used now.

Denosumab
Denosumab, the human monoclonal antibody against RANK ligand, was shown to delay the time to development of hypercalcemia of malignancy in clinical studies, but its role in treating hypercalcemia of malignancy needs to be further investigated [133].

Calcimimetics
Among calcimimetic agents, cinacalcet has been shown to reduce calcium levels in primary [119–122] or secondary hyperparathyroidism in hemodialysis patients [134] and parathyroid carcinoma [127]. Cinacalcet is FDA approved for the treatment of hypercalcemia in patients with parathyroid carcinoma and patients with PHPT who have severe hypercalcemia and are unable to undergo parathyroidectomy [124].

Dialysis
This is useful in severe, life-threatening hypercalcemia or in cases in which immediate serum calcium reduction is needed and IV infusion of saline or bisphosphonates are contraindicated. However, hypercalcemia recurs quickly after dialysis stops.

Hypercalcemic Emergencies
Symptomatic individuals with hypercalcemia should be admitted to the hospital for immediate treatment. Aggressive hydration with IV fluids should be initiated regardless of the etiology of hypercalcemia. If the cause is increased bone resorption, such as PHPT or metastatic bone disease, or immobilization of a Pagetic patient, IV bisphosphonates (i.e., pamidronate at 60–90 mg IV over a 4- to 6-hour period or zoledronic acid at 4 mg IV over a 15-minute period) can be given. If the etiology is due to vitamin D toxicity or excess states (lymphoma, sarcoidosis, milk-alkali), bisphosphonates do not have a significant impact, as bone resorption is usually not the main mechanism. Hydration would be the main modality. Steroids can be tried for sarcoidosis.

It takes a few days for IV bisphosphonates to have an effect. Calcitonin, 100 IU subcutaneously, can be used for a few days while waiting for the bisphosphonates to work. Diuresis can be tried with IV or oral furosemide but only after significant reduction in calcium is not achieved with any of these measures and only once the patient is volume replete.

Future Therapy
22-Oxocalcitriol and EB 1089, an analogue of calcitriol, were found during in vitro studies to suppress PTH-related protein gene expression [135].

HYPOCALCEMIA

Diagnosis

The diagnosis of hypocalcemia should be confirmed by measurement of ionized calcium. Other tests that are useful in determining the etiology include intact PTH, phosphate, 25(OH)D, $1,25(OH)_2D$, magnesium, creatinine, alanine aminotransferase (ALT), and total or BSAP. Common causes are shown in Table 4.12.

In adults, hypoparathyroidism is frequently a result of thyroid or parathyroid surgery. Presentation during childhood raises the possibility of congenital hypoparathyroidism or pseudohypoparathyroidism (Table 4.12). Whether congenital or acquired, hypoparathyroidism is first seen with a low serum calcium and a low or inappropriately normal PTH level (Table 4.13). Phosphate levels may be normal or high. A syndrome of hypocalcemia with hypercalciuria due to an abnormal calcium-sensing receptor gene has been reported [136].

If vitamin D metabolite levels are low, the cause should be determined by history and examination. One should look for rickets, osteomalacia, malabsorption, hepatic disease, renal insufficiency, and medications that interfere with vitamin D metabolism, such as phenytoin. Serum phosphate levels may be low or low normal, and urinary excretion of calcium may be low. A bone biopsy is the gold standard for diagnosing osteomalacia; however, an elevation in BSAP in an individual with vitamin D or calcium deficiency and secondary hyperparathyroidism usually suggests the disease.

Hypomagnesemia causes hypocalcemia through failed PTH secretion or bone resistance to PTH at exceedingly low concentrations. Serum levels may be normal despite low tissue levels seen in association with chronic malabsorption and alcoholism.

In hospitalized patients, hypocalcemia can develop from diuretics, blood transfusions, chemotherapy, and other concomitant illnesses such as sepsis, pancreatitis, acute renal failure, and hemodialysis.

Treatment

Hypocalcemic Emergencies

Symptomatic hypocalcemia, particularly in those patients with tetany, seizures, electrocardiographic changes, and decreased cardiac function, should be treated with IV calcium. Calcium gluconate, as a bolus of 1 to 2 g, provides 100 to 200 mg elemental calcium, followed by a continuous drip at 0.5 to 1.5 mg/kg/h. Calcium gluconate is preferred over the highly alkaline calcium chloride because it produces less local tissue necrosis. Calcitriol should be started immediately at a loading dose of 1.0 μg, followed by 0.5 μg daily with reduction, generally to 0.25 μg over a few days as the calcium deficiency is resolved. Once stabilized and able to take oral

Table 4.12. Common Causes of Hypocalcemia

Hypoparathyroidism	Hungry-bone syndrome following parathyroidectomy
Pseudohypoparathyroidism	Bisphosphonates
Nutritional hypovitaminosis D	Fluoride poisoning
Malabsorption	Concomitant illnesses: sepsis, surgery, chemotherapy, tumor lysis syndrome, renal failure
Hypomagnesemia	
Vitamin D–dependent rickets type 1 and 2	
Intravascular and extravascular calcium deposition	

Table 4.13. Clinical Manifestations of Hypocalcemia

Musculoskeletal	***Ocular***
Tetany, muscle cramps and spasms, myopathy, circumoral and acral paresthesia	Cataracts
Trousseau sign: carpal spasm with inflation of blood pressure cuff to above systolic	Keratoconjunctivitis
Chvostek sign: facial muscle contraction when the facial nerve is tapped on the ipsilateral side, anterior to the ear	Papilledema with severe hypocalcemia
	Cardiovascular
Neuropsychiatric	Hypotension
Seizures, fatigue, depression, anxiety, lethargy, mental retardation in children	Myocardial dysfunction
	Congestive heart failure
	Prolonged QT interval
	Decreased digitalis effect
Movement Disorders	***Gastrointestinal***
Dystonia, hemiballismus	Steatorrhea
Basal ganglia calcifications	Decreased gastric acid secretion
	Skin
	Dry and coarse skin and hair, brittle hair and nails

medications, the patient may be started on calcium supplements and calcitriol continued.

Oral Calcium Supplements

The goal of treatment in chronic hypocalcemia is to maintain serum calcium in the low-normal range. The elemental calcium dose required is quite variable and generally ranges from 1.5 to 3.0 g daily in divided doses (t.i.d or q.i.d), usually with an active vitamin D analogue. In hypoparathyroidism, the absorption of oral calcium is very low (thus the reason for large amounts described earlier). Various preparations of oral calcium are available. Calcium carbonate (250 mg elemental calcium per 600 mg tablet) is the least expensive, but it has poor absorption in patients with low gastric acid production. Ultradense calcium citrate (315–500 mg elemental calcium per tablet) is preferred except in patients with renal failure. One must remember that the elemental calcium content of calcium lactate and gluconate tablets is very low. Because most of these patients will be taking supraphysiologic doses of vitamin D, the authors caution readers that hypercalciuria, usually in the setting of normocalcemia, may exist. Urine calcium excretion should be monitored frequently, even biannually in very stable patients. Should hypercalciuria be found, defined as more than 300 mg/24 hr, it is important to reduce the supplementation, particularly of the vitamin D.

Vitamin D

Various forms of vitamin D are available—ergocalciferol (vitamin D_2), cholecalciferol (vitamin D_3), dihydrotachysterol, 1-α-hydroxyvitamin D_3, and calcitriol (1-25 dihydroxyvitamin D_3). Ergocalciferol and calcitriol are the most frequently used. Ergocalciferol is available in 50,000-IU capsules, an 8,000-IU/ml liquid form, or a 500,000-IU/ml infusion. Because this form of vitamin D must be activated, intact hepatic and kidney function are necessary. Patients with renal failure

and hypoparathyroidism need to receive supplementation with calcitriol. This is available in 0.25- and 0.5-μg capsules. It is the most rapid-acting metabolite of vitamin D. Hypercalcemia and hypercalciuria can occur, more commonly with calcitriol. Thus, urinary and serum calcium levels should be monitored at least biannually. The goal is to maintain a low-normal serum calcium concentration and normal calcium excretion.

Calcidiol [25(OH)D] is available in 20- and 50-mg capsules. Action is more rapid, but it is not as prolonged as with vitamin D dihydrotachysterol (the equivalent of $1(OH)_2D$), which requires 25-hydroxylation in the liver.

One study that compared the calcium-absorptive effects of calcitriol, calcidiol, and cholecalciferol found the potency of calcitriol and calcidiol to be 100:1. Vitamin D_3, or cholecalciferol, was the least potent in increasing calcium absorption [137]. However, a meta-analysis showed greater beneficial effects of hydroxylated vitamin D on BMD than of nonhydroxylated vitamin D [80].

Newer analogues of vitamin D, paricalcitol and doxercalciferol, have become available. They are both indicated for patients with advanced renal insufficiency, both providing the advantage of avoiding increases in the calcium/phosphorus product that may lead to deleterious effects. Both products effectively reduce PTH levels without causing significant hypercalcemia and hypercalciuria [136,137]. However, in situations in which the goal is to improve calcium absorption and increase calcium levels, calcitriol, ergocalciferol, or cholecalciferol would be preferred over these two newer analogues.

Magnesium

Concomitant magnesium deficiency should be corrected, provided that renal function is normal. The starting dose may be 2 g of magnesium sulfate given as an IV bolus over a 10-minute period, followed by 1 g/h if necessary. Once the patient is replete, maintenance therapy may be initiated with oral magnesium supplements.

Parathyroid Hormone

It seems logical that PTH would be beneficial in treating hypoparathyroidism. However, few studies are available that have looked at this treatment possibility. One such trial randomized 20 patients with hypoparathyroidism to PTH twice a day or calcium and calcitriol. The patients taking PTH required about 37 μg, and those taking calcitriol needed 0.91 μg to attain normal calcium concentrations. Calcium, phosphorus, and magnesium levels did not differ between the groups. PTH normalized urine calcium levels, whereas calcitriol did not. No significant changes were seen in BMD between the groups. BTMs increased more in the PTH group. Many subjects preferred injection to the pills [138]. PTH, however, does not have the FDA indication for hypoparathyroidism.

OSTEOMALACIA

Osteomalacia refers to a defect in mineralization of bone matrix or osteoid, which can have various causes. Congenital deficiencies typically demonstrate classic findings during infancy and childhood. In contrast, osteomalacia in adults is frequently detected as low bone mass and biochemical abnormalities. Those with more severe disease may have bone pain, spontaneous pelvic fractures, pseudofractures, and muscle weakness. Laboratory evaluation reveals low 25(OH)D concentrations and frequently decreased serum calcium, phosphate, and 24-hour urinary calcium. Most patients have secondary hyperparathyroidism, and in general, the lower the vitamin D concentration, the higher the PTH concentration [139,140].

The exact concentrations of 25(OH)D seen with various bone changes such as osteoporosis and osteomalacia are still not entirely clear but are becoming more defined. Concentrations over 30 ng/ml are generally considered sufficient. Those

between approximately 8 and 30 ng/ml are insufficient, with increased fracture risk and decreased calcium absorption. Concentrations less than 8 ng/ml may be associated with osteomalacia. One issue plaguing this is the lack of standardization and the variability of 25(OH)D assays [141].

Osteomalacia related to hypovitaminosis D is treated with supplementation of vitamin D and calcium. A gluten-free diet in celiac sprue usually improves calcium and vitamin D absorption, leading to reduced requirements for these agents. Treatment recommendations for vitamin D repletion are discussed in the Section on Vitamin D Deficiency. Serum calcium, intact PTH, and urinary calcium should be monitored every 3 months until they normalize and at regular 6 to 12 months intervals thereafter, as hypercalcemia and hypercalciuria can happen.

Vitamin D–Dependent Rickets (Type 1 and Type 2)

These are rare congenital errors of vitamin D metabolism. Type 1 rickets is an autosomal recessive disorder that results in a defect in renal tubular 25(OH)D-1α-hydroxylase. It usually presents with rickets and signs of hypocalcemia during the first 2 years of life. Calcium and $1,25(OH)_2D$ levels are low, 25(OH)D levels may be normal or low, and intact PTH levels are elevated. Calcitriol in the dose of 0.25 to 1 μg/d is usually enough to correct the deficit. Careful monitoring of serum calcium, urinary calcium, and intact PTH should be used to titrate the dose.

Type 2 rickets, however, is a hereditary condition that results in resistance to the effects of $1,25(OH)_2D$. Usually, the disease is first seen during infancy, before age 2 years, but reports have been made of the disorder in adults [142,143]. Calcium levels have been normal in patients with the first appearance later in life. It can be distinguished from type 1 rickets by normal or elevated $1,25(OH)_2D$ levels. Similarly, 25(OH)D levels may be normal, or low and intact PTH levels are elevated. Large doses of calcitriol (30–60 mg/d) are necessary to correct hypocalcemia and to induce mineralization of bones.

Oncogenic Osteomalacia

This condition is usually associated with mesenchymal tumors and remits after tumor excision. Osteomalacia is most likely due to oversecretion of fibroblast growth factor 23 (FGF23), a phosphaturic hormone, by the mesenchymal tumor. Findings supporting this theory include elevated serum concentrations of the FGF23 that normalize after resection of the tumor, the detection of FGF23 and its mRNA in the offending mass, and a preoperative defect in renal phosphate reabsorption, which subsequently improves after surgery [144,145]. These mesenchymal tumors are most commonly present in the head and neck or in the lower extremities [146]. Patients can have symptoms for months to years, with complaints of muscle weakness, bone pain, or recurrent fractures. Biochemical findings include hypophosphatemia and low tubular reabsorption of phosphorus [147,148]. A thorough search for the tumor must be undertaken with radiographs or MRI. Technetium scanning and F-18 FDG PET have also been used in localizing the tumors [149,150]. Treatment consists mainly of excision of the tumor. Some investigators have also found improvement of the disease with calcitriol and phosphorus supplementation [151].

Hypophosphatemic Rickets

This X-linked disorder results in decreased renal tubular reabsorption of phosphorus. So-called classic cases involve male patients with low phosphorus levels, stunted growth, and lower limb deformities. However, cases of mild isolated hypophosphatemia have been seen in women who are heterozygous for the gene known as PHEX. Optimal treatment involves phosphorus and calcitriol [151].

Growth hormone therapy has had positive effects on growth in children afflicted with the disorder [152,153]. Twelve months of growth hormone supplementation

has improved height and growth velocity SD scores compared with those with placebo [152].

Hypophosphatasia

This rare disorder results from decreased tissue-nonspecific ALP activity. Presentation may be severe during childhood or mild during adulthood. Adult hypophosphatasia can present with recurrent stress fractures, painful hips, or pseudofractures [154]. Affected individuals usually have low ALP levels, normal or high levels of calcium and phosphate, high phosphoethanolamine, and high inorganic pyrophosphate (Ppi). Measurement of pyridoxal 5′-phosphate is the most sensitive and specific test for hypophosphatasia. No approved medical treatment is known for this condition. Vitamin D and calcium supplementation could produce more harm than good because associated calcium and vitamin D levels are not low. Teriparatide has been reported to reduce pain, improve mobility, and promote fracture healing in adult patients with hypophosphatasia with various effects on biochemical markers demonstrated [155–158]. Further studies should be conducted regarding the benefits and risks of this application of teriparatide.

Drug-Induced Osteomalacia

Commonly used drugs that can cause osteomalacia include anticonvulsants (inhibition of 25-hydroxylation), cholestyramine (reduced absorption), glucocorticoids (inhibition of the vitamin D action), aluminum-containing antacids (inhibition of phosphate absorption), and etidronate (inhibition of osteoblast activity). Treatment consists of discontinuation of the offending agents.

VITAMIN D DEFICIENCY

The essential role of vitamin D in normal bone health across all age spectra is well known and recognized. More evidence is emerging on the importance of vitamin D in nonskeletal health, including the CV, immunologic, and neurologic systems.

Sources of Vitamin D

There are three main sources of vitamin D in humans [159]:

- Sunlight exposure: Previtamin D_3 is synthesized in the human skin by conversion from 7-dehydrocholesterol via the effect of ultraviolet radiation. It then undergoes hydroxylation in the liver to 25-hydroxyvitamin D and a second hydroxylation via the kidney's 1α-hydroxylase to the active form, 1,25-dihydroxyvitamin D.
- Diet: Sun-dried shiitake mushrooms; fresh, wild salmon; and cod liver oil are the three richest natural sources of vitamin D. Several foods especially dairy products, orange juice, and cereals are also fortified in vitamin D.
- Dietary supplements: These include multivitamins and various over-the-counter and prescribed vitamin D supplements.

Prevalence

Vitamin D deficiency is a highly prevalent condition, with an estimated 1 billion people having lower than optimal vitamin D levels in the world. The prevalence varies depending on the studied population, ranging from 30% to 100% across various age groups, ethnicities, and geographic locations [159]. Data from the 2001 to 2004 NHANES population show that 70% of US children and adolescents ages 1 to 21 have vitamin D deficiency or insufficiency [160]. Among healthy young adults, 36% were found to have vitamin D deficiency after the winter season in one study [161]. In a study on women being treated for osteoporosis in the United States, approximately half were found to have vitamin D deficiency or

insufficiency [140]. Another study showed a vitamin D deficiency prevalence of approximately 50% among hospitalized individuals [162].

Risk Factors

Older age, black race, winter season, and low vitamin D intake were found to be associated with low 25-hydroxyvitamin D levels in healthy US children and adolescents [163]. In an NHANES subpopulation, higher body mass index (BMI), lower milk consumption, and sun protection were associated with decreasing vitamin D levels [164]. Other risk factors for vitamin D deficiency include living in northern latitudes, fat malabsorption syndromes, advanced liver failure, nephrotic syndrome, and medications that increase vitamin D catabolism such as antiepileptic medications and corticosteroids [159].

Skeletal Effects

The active form of vitamin D stimulates intestinal calcium and phosphorus absorption, glomerular calcium reabsorption, and osteoclast activation to mobilize calcium from the bones. Vitamin D deficiency results in poor calcium absorption, which in turn stimulates PTH production. Elevated PTH levels maintain normocalcemia by activating osteoclasts and mobilizing calcium from the bones, at the expense of BMD, which then decreases. Impaired phosphorus absorption, as well as the PTH-mediated phosphaturia, leads to a low phosphorus state, which may result in deficient bone mineralization [165]. Therefore, vitamin D deficiency in children may cause rickets, whereas in adults, it may cause osteomalacia, or worsening of osteopenia or osteoporosis [166]. There is some evidence that BMD is directly correlated with vitamin D levels. In patients with vitamin D deficiency, normalization of vitamin D levels is associated with a lower fracture risk, a lower fall risk, and an improvement in proximal muscle strength [159,167–169]. Vitamin D receptors are also found in skeletal muscle, and vitamin D deficiency may result in proximal muscle weakness [166].

Nonskeletal Effects

Vitamin D receptors have been identified in several tissues besides the skeletal system, and these include brain, prostate, breast, colon, and immune cells. The active form of vitamin D has actually been involved in cell cycle regulation, cellular differentiation and apoptosis, immune modulation, renin synthesis, insulin production, and myocardial contractility [159,170]. In Framingham Offspring Study participants, patients with low 25-hydroxyvitamin D had a higher risk of developing CV events, and the risk seemed to increase as vitamin D levels decreased [171]. In a cohort of patients undergoing coronary angiography, low 25-hydroxyvitamin D levels were independent predictors of all-cause and CV mortality [172]. In adolescents from the 2001 to 2004 NHANES database, low vitamin D was associated with a higher risk of hypertension, fasting hyperglycemia, and metabolic syndrome [173]. Vitamin D deficiency is associated with a higher incidence of and mortality related to certain cancers such as Hodgkin lymphoma, colon, prostate, ovarian, breast, and other cancers [159,165,166]. Studies have also shown that a higher vitamin D intake reduces the risk of type 1 and type 2 DM, multiple sclerosis, RA, and osteoarthritis and results in significant clinical improvement in patients with psoriasis [159,165,170]. In addition, elderly people with vitamin D deficiency were found to have a higher risk of cognitive decline compared with those who were vitamin D replete [174]. In animal studies, vitamin D deficiency was also linked to inflammatory bowel disease, systemic lupus erythematosus, and transplant rejection [170]. Other disorders that have been linked to vitamin D deficiency include hypertension, congestive heart failure, schizophrenia, depression, and wheezing illnesses [159].

Clinical Presentation

Vitamin D deficiency may be asymptomatic, especially in patients with marginally low 25-hydroxyvitamin D levels. However, patients with vitamin D deficiency may present with bone pains, usually described as throbbing, aching pains, muscle weakness, and generalized fatigue. On examination, patients may have bony tenderness especially along the sternum or the tibiae, proximal muscle weakness, and hyperreflexia due to poor calcium malabsorption and negative calcium balance. Classic rickets or bowing of the tibia is less common [159].

Diagnosis

Vitamin D nutritional status is best assessed by measuring a 25-hydroxyvitamin D level. Although 1,25-dihydroxyvitamin D is the active form, it cannot be used to assess for vitamin D sufficiency because of its short half-life and the fact that it can be maintained in the normal range in vitamin D–deficient states, due to activation of the kidney's 1-α-hydroxylase by the resultant secondary hyperparathyroidism [175]. Vitamin D deficiency is defined as a 25-hydroxyvitamin D level lower than 20 ng/ml, whereas vitamin D insufficiency is defined as 25-hydroxyvitamin D level that is less than 30 ng/ml but higher than 20 ng/ml [166]. Other biochemical features of vitamin D deficiency include secondary hyperparathyroidism, low urinary calcium levels, and elevated ALP levels. Patients with osteomalacia usually have distinct radiologic findings, particularly Looser lines or pseudofractures.

Treatment

Goals of therapy are restoring normal 25-hydroxyvitamin D levels and correcting the associated secondary hyperparathyroidism. It has been estimated that 25-hydroxyvitamin D levels of at least 30 ng/ml and preferably between 36 and 40 ng/ml are optimal with regard to improving several health outcomes [176]. Vitamin D deficiency can be treated with vitamin D_2 or D_3 50,000 IU weekly for 8 to 12 weeks [159]. The course can be continued if goals of therapy have not been reached. Some patients especially those with underlying malabsorptive disorders may require higher doses to correct their deficiency. Once 25-hydroxyvitamin D and PTH levels are in the normal range, patients can then be transitioned to maintenance dose.

It is recommended that the maintenance dose for infants should be at least 400 IU of vitamin D daily [177]. As for older children and adults, several experts agree that the maintenance dose should be at least 800 to 1,000 IU vitamin D daily [166]. In a 2010 report from the IOM, the recommended daily allowance of vitamin D for the general healthy population was 600 IU daily, except for people who are 71 years or older, who may require up to 800 IU daily [178].

Controversy exists regarding vitamin D replacement in hyperparathyroid patients. In patients with PHPT and mild hypercalcemia, vitamin D replacement with doses up to 50,000 IU twice weekly did not result in worsening hypercalcemia, improved PTH levels in some cases, but seemed to cause hypercalciuria in up to one-third of patients [179]. In patients with mild PHPT, cautious vitamin D replacement with close monitoring of 24-hour urine calcium levels is recommended.

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   Urinary excretion of cross-linked *N*-telopeptides of type 1 collagen was obtained from 65 early postmenopausal women who participated in a placebo-controlled trial of the aminobisphosphonate alendronate sodium. Intersubject variability for cross-linked peptide excretion was 20.2% over the 9 months in placebo-treated subjects, substantially lower than that observed for other biochemical markers of bone resorption: 45%, 53%, and 63% for fasting urinary calcium and hydroxyproline and 24-hour urinary lysylpyridinoline (by HPLC assay), respectively. Baseline cross-linked peptide excretion correlated significantly ($p < 0.001$) with baseline total urine lysylpyridinoline and serum osteocalcin but not with other biochemical markers. Initial peptide excretion also correlated inversely with LS BMD at entry ($r = -0.26$; $p < 0.05$). Alendronate treatment for 6 weeks produced a dose-dependent suppression of cross-linked peptide excretion (0% ± 8%, 29% ± 6%, 56% ± 5%, and 64% ± 3% for 0, 5, 20, and 40 mg, respectively; $p < 0.01$ vs. placebo for treatment effect), with a return toward pretreatment values during follow-up.

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   The Malmo Osteoporosis Prospective Risk Assessment study was a longitudinal population-based study that examined seven BTMs in 1,044 women at 1, 3, and 5 years, as well as BMD at 5 years, to identify women with the highest risk for bone loss. The study found that women with constantly high turnover lost significantly more bone compared to women with intermediate or low as well as greater decrease in hip BMD.

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   This was a 2-year, randomized, controlled study of 236 healthy women at 1 to 3 years after menopause. Women received estrogen plus progesterone plus calcium (treated group) or calcium alone (control group). In the treated group, NTX significantly decreased ($p < 0.0001$), and spine and hip BMD significantly increased ($p < 0.00001$ and $p < 0.005$, respectively); in the control group, NTX did not change but BMD decreased significantly ($p < 0.01$). Subjects in the highest quartiles for baseline NTX (67–188 U) or decreasing NTX (−66%–87%) through 6 months demonstrated the greatest gain in BMD in response to HRT ($p < 0.05$ and $p < 0.005$). For every increase of 30 U in baseline NTX, the odds of gain in BMD in response to HRT increased by a factor of 5.0 (CI, 1.9–13.3); for every 30% decrease in NTX through 6 months, the odds of gaining BMD in response to HRT increased by a factor of 2.6 (CI, 1.6–4.4). In the control group, an increase of 30 U in mean NTX across the study indicated higher odds of losing BMD by a factor of 3.2 (CI, 1.6–6.5). A high baseline NTX (67 U) indicated a 17.3 times higher risk of BMD loss if not treated with HRT.

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   In this trial, 373 women who were 65 years of age and older were randomized to alendronate, HRT, a combination of the two, or placebo and then followed up for 3 years, with NTX, BSAP, and osteocalcin levels determined every 6 months. A positive correlation was demonstrated between a decrease in the bone markers at month 6 and an increase in BMD at the spine and hip at the end of the study, in the patients taking the active medications. Those taking alendronate had greater decreases in bone markers and increases in BMD than did those receiving HRT. With respect to specific bone markers, the tertile that had the greatest decrease in NTX was associated with BMD increases of 10.1% at the spine and 6.1% at the hip as compared with the lowest tertile, which had BMD increases of 5.9% at the spine and 2.1% at the hip.

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In this study, baseline bone markers in healthy untreated postmenopausal women between the ages of 50 and 89 years (mean, 64 years) who sustained a fracture were compared to those who did not have a fracture during over 5 years of follow-up. Women with levels in the highest quartile of four bone-resorption markers including urinary free deoxypyridinoline, urinary type 1 collagen *N*-telopeptides, and urinary and serum type 1 collagen C-telopeptides had about a two-fold increased risk of fractures compared with women with levels in the three lowest quartiles. Serum levels of bone ALP in the highest quartile were associated with an RR of fracture of 2.4. Adjustment of biochemical markers by hormone levels did not significantly alter the results. Bone markers were still predictive of fracture risk even after adjusted for BMD.

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   This is a prospective cohort study of 7,598 healthy women 75 years and older. The group comprised 126 women who sustained a hip fracture during a mean 22-month follow-up who were age-matched with three controls who did not experience fracture. Elderly women had higher markers of bone formation and resorption than did healthy premenopausal women. CTX and free deoxypyridinoline, but not other markers, were higher in patients with hip fracture ($p = 0.02$ and 0.005, respectively). CTX and free deoxypyridinoline excretion above the premenopausal range was associated with an increased hip fracture risk with an odds ratio of 2.2 (CI, 1.3–3.6) and 1.9 (CI, 1.1–3.2), respectively, whereas markers of formation were not. Increased bone resorption was an independent predictor of hip fracture. Women with both a femoral *T*-score of −2.5 or less and either high CTX or high free deoxypyridinoline levels were at greater risk of hip fracture, with odd ratios of 4.8 and 4.1, respectively, than were those with only low BMD or high bone resorption.

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    BSAP, PINP, and PICP were measured in the 6,186 participants of the FIT after 1 year of exposure to alendronate or placebo, and the results were analyzed with respect to fractures that occurred during the trial. A significant positive association was seen. A decrease in BSAP by one SD was linked to less spine (26% reduction; CI, 12%–37%), nonspine (14% reduction; CI, 2%–24%), and hip fractures (40% reduction; CI, 21%–55%).

Bone Imaging

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    This is a meta-analysis of 12 studies, consisting of 9,891 men and 29,082 women in total. It sought to find the correlation between BMD and fracture risk, as well as the influence of such factors as age, gender, and initial BMD. At age 65 years, an SD decrease in BMD increased the risk ratio for hip fracture by 2.94 (CI, 2.02–4.27) in men and 2.88 (CI, 2.31–3.59) in women. In addition, the risk for all fragility fractures increased by 1.41 (CI, 1.33–1.51) in men and 1.38 (CI, 1.28–1.48) in women.

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    This observational study assessed the lateral spines of 342 subjects by DXA. Fifty of the three hundred forty-two patients (14.6%; CI 11%–18.8%) had at least one vertebral compression deformity. 21.3% of the study population (73 of 342) were at least 60 years old and osteopenic by *T*-score criteria; 27 of these 73 subjects (27.4%) had at least one vertebral deformity.

Osteoporosis

13. (1) **Black DM, Cummings SR, Karpf DB,** et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. Lancet 1996;348:1535–1541.

    This is a randomized, placebo-controlled trial of 2,027 postmenopausal women aged between 55 and 81 years with low femoral neck BMD who were assigned to receive placebo ($n = 1,005$) or

daily alendronate (n = 1,022) and were observed during a follow-up for 36 months. Alendronate reduced the risk of new radiographic fractures by 47%. Clinically apparent vertebral fractures were reduced in the alendronate group (2.3% vs. 5.0%; RH, 0.45; CI, 0.27–0.72). The risk of any clinical fracture was lower in the alendronate group than in the placebo group (139 [13.6%] vs. 183 [18.2%]; RH 0.72 [0.58–0.90]), including a 51% reduction in hip fractures. No significant differences in the number of adverse events in the two groups were seen.

14. (1) **Cummings SR, Black DM, Thompson DE,** et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. JAMA 1998;280:2077–2082.

    A prospective, double-blind, randomized, placebo-controlled study of 4,432 postmenopausal women aged between 54 to 81 years without preexisting vertebral fractures who were randomly assigned to receive alendronate or placebo and followed up for 4 years. Similar to FIT 1, alendronate was initially given at 5 mg/d for 2 years followed by 10 mg/d. Alendronate increased BMD at all sites studied ($p < 0.001$). Risk of radiographic vertebral fracture was reduced by 44% (relative risk, 0.56; 95% CI, 0.39–0.80; treatment-control difference, 1.7%; number needed to treat [NNT], 60). Clinical vertebral fracture reduction was not significantly different; however, in the subset of patients with femoral neck T-scores of −2.5 or less, alendronate reduced clinical vertebral fractures by 36% (RH, 0.64; 95% CI, 0.50–0.82; treatment-control difference, 6.5%; NNT, 15).

15. (1) **Cranney A, Wells G, Willan A,** et al. Meta-analyses of therapies for postmenopausal osteoporosis. II. Meta-analysis of alendronate for the treatment of postmenopausal women. Endocr Rev 2002;23:508–516.

    This was a meta-analysis of 11 randomized, placebo-controlled trials of alendronate for postmenopausal osteoporosis. The pooled RR for vertebral fracture for the 5-mg dose was 0.52 (95% CI, 0.43–0.65), and for the nonvertebral fracture RR for 10 mg or more was 0.51 (CI, 0.38–0.69). Results for nonvertebral fractures were similar. Two- to four-year percentage increases in BMD between alendronate and placebo were 7.48% (CI, 6.12–8.85) for the LS, 5.6% (CI, 4.8–6.39) for the hip, 2.08% for the forearm (CI, 1.53–2.63), and 2.73% (CI, 2.27–3.2) for the total body. Pooled RR for gastrointestinal side effects was 1.03 (0.81–1.3; $p = 0.83$).

16. (1) **Papapoulos SE, Quandt SA, Liberman UA, Hochberg MC, Thompson DE.** Meta-analysis of the efficacy of alendronate for the prevention of hip fractures in postmenopausal women. Osteoporos Int 2005;16:468–474.

    This was a meta-analysis of six randomized trials of alendronate that lasted from 1 to 4.5 years. At least 95% received 5 to 10 mg of alendronate daily. The subjects with a vertebral fracture or T-scores greater than or equal to −2.0 who were taking alendronate had a hip-fracture RR of 45% (CI, 16%–64%; $p = 0.007$); those with osteoporosis by T-score had a 55% reduced risk (CI, 29%–72%; $p = 0.0008$).

17. (1) **Black DM, Schwartz AV, Ensrud KE,** et al. Effects of continuing or stopping alendronate after 5 years of treatment: The Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. JAMA 2006;296:2927–2938.

    The FLEX trial was a randomized, double-blind, placebo-controlled trial that included 1,099 postmenopausal women who had been randomized to alendronate in FIT. The patients were randomized to receive alendronate or placebo for 5 years. The primary outcome was total hip BMD. Fracture incidence was an exploratory outcome measure. The total hip BMD increased by 2.41% in the group who received alendronate in the FIT and FLEX trial compared to a decrease of 0.16% in the group who received placebo in the FLEX trial. There was no significant difference between the groups for all clinical fractures or nonvertebral fractures. There was a 55% relative RR in clinical vertebral fractures in those who received alendronate compared to placebo. However, it is important to note that while there was a moderate decline in BMD and a gradual rise in BTMs in the group that discontinued alendronate, both remained above baseline values and there was not a higher risk of fracture other than for clinical vertebral fractures compared to those who continued alendronate. These results suggest that there is residual effect of alendronate for up to 5 years after discontinuing the medication.

18. (1) **Schnitzer T, Bone HG, Crepaldi G,** et al. Therapeutic equivalence of alendronate 70 mg once-weekly and alendronate 10 mg daily in the treatment of osteoporosis. Alendronate Once-Weekly Study Group. Aging (Milano) 2000;12:1–12.

    The efficacy and safety of treatment with oral once-weekly alendronate, 70 mg, twice-weekly alendronate, 35 mg, and daily alendronate, 10 mg, were compared in a 1-year, double-blind, multicenter study of postmenopausal women with osteoporosis by T-score or previous vertebral or hip fracture. Mean increases in LS BMD at 12 months were 5.1% (CI, 4.8–5.4) in the 70-mg once-weekly group, 5.2% (CI, 4.9–5.6) in the 35-mg twice-weekly group, and 5.4% (CI, 5.0–5.8) in the 10-mg daily-treatment group. Increases in BMD at the total hip, femoral neck, trochanter, and total body were similar for the three groups. Reduction in markers of bone resorption (urinary NTX) and bone formation (serum BSAP) were similar across three groups into the middle

of the premenopausal reference range. Upper gastrointestinal adverse experiences were similar, with a trend toward a lower incidence of esophageal events in the once-weekly dosing group.

19. (1) **Orwoll E, Ettinger M, Weiss S,** et al. Alendronate for the treatment of osteoporosis in men. N Engl J Med 2000;343:604–610.

    This is a 2-year, double-blind, placebo-controlled trial. The effect of daily alendronate (10 mg) or placebo on BMD in 241 men with osteoporosis was evaluated. About one-third had low serum free testosterone concentrations at baseline; the rest had normal concentrations and no other secondary causes of osteoporosis. The men who received alendronate had a mean (±standard error of the mean (SEM)) increase in BMD of 7.1% ± 0.3% at the LS, 2.5% ± 0.4% at the femoral neck, and 2.0% ± 0.2% for the total body ($p < 0.001$ for all comparisons with baseline). In contrast, men who received placebo had an increase in LS BMD of 1.8% ± 0.5% ($p < 0.001$ for the comparison with baseline) and no significant changes in femoral neck or total body BMD. Vertebral fracture incidence was lower in the alendronate group than in the placebo group (0.8% vs. 7.1%; $p = 0.02$), and height loss was significantly greater in the placebo than alendronate group (2.4 vs. 0.6 mm; $p = 0.02$).

20. (1) **Saag KG, Emkey R, Schnitzer TJ,** et al. Alendronate for the prevention and treatment of glucocorticoid-induced osteoporosis. Glucocorticoid-Induced Osteoporosis Intervention Study Group. N Engl J Med 1998;339:292–299.

    Two 48-week, randoimized, placebo-controlled studies of two doses of alendronate were conducted on 477 men and women taking glucocorticoids. The mean BMD of the LS increased by 2.1% ± 0.3% and 2.9% ± 0.3% in the groups that received 5 and 10 mg of alendronate per day, respectively ($p < 0.001$), and decreased by 0.4% ± 0.3% in the placebo group. The femoral neck bone density increased by 1.2% ± 0.4% and 1.0% ± 0.4% in the respective alendronate groups ($p < 0.01$) and decreased by 1.2% ± 0.4% in the placebo group ($p < 0.01$). The BMD of the trochanter and total body also increased significantly in the patients taking alendronate. There were proportionally fewer new vertebral fractures in the alendronate groups (overall incidence, 2.3%) than in the placebo group (3.7%; RR, 0.6; CI, 0.1–4.4). Markers of bone turnover decreased significantly in the alendronate groups ($p < 0.001$). There were no differences in serious adverse effects among the three groups, but there was a small increase in minor upper gastrointestinal effects in the 10-mg group.

21. (1) **Rosen CJ, Hochberg MC, Bonnick SL,** et al. Treatment with once-weekly alendronate 70 mg compared with once-weekly risedronate 35 mg in women with postmenopausal osteoporosis: a randomized double-blind study. J Bone Miner Res 2005;20:141–151.

    This randomized, double-blind, active-controlled, multicenter trial assessed BMD and BTM changes, as well as side effects, in 1,053 postmenopausal osteoporotic women who were randomized to alendronate, 70 mg weekly, or risedronate, 35 mg weekly, for 12 months. At 1 year, those taking alendronate had small but significant increases in BMD over the subjects taking risedronate, with treatment differences of 1.4% at the trochanter (CI, 0.8%–1.9%; $p < 0.001$), 1.1% at the hip (CI, 0.7%–1.4%; $p < 0.001$), 0.7% at the femoral neck (0.1%–1.2%; $p = 0.005$), and 1.2% at the LS (CI, 0.7%–1.6%; $p < 0.001$). Significant differences at all sites in BMD were seen at 6 months as well. More patients (10.3%) in the alendronate group demonstrated at least a 3% increase in trochanter BMD at 1 year (CI, 4%–16.7%; $p = 0.002$), and 16.7% more patients taking alendronate than risedronate exhibited a maintenance of or gain in trochanter BMD at 12 months ($p < 0.001$). CTX, NTX, BSAP, and PINP were all depressed more with alendronate ($p < 0.001$). No significant differences in adverse events were noted between the two groups.

22. (1) **Harris ST, Watts NB, Genant HK,** et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. JAMA 1999;282:1344–1352.

    In this randomized, double-blind, placebo-controlled trial, 2,458 postmenopausal women younger than 85 years and with at least one vertebral fracture were randomly assigned to receive 3 years of risedronate (2.5 or 5 mg/d) or placebo. All subjects received calcium (1,000 mg/d), and cholecalciferol (≥500 IU/d) was provided if baseline levels of 25(OH)D were low. The 2.5 mg/d of the risedronate arm was discontinued after 1 year. Treatment with 5 mg/d of risedronate decreased the incidence of new vertebral fracture risk by 41% (CI, 18%–58%) over a 3-year period (11.3% vs. 16.3%; $p = 0.003$). Vertebral fracture reduction of 65% (CI, 38%–81%) was seen after the 1st year (2.4% vs. 6.4%; $p < 0.001$). Nonvertebral fracture incidence over a 3-year period was reduced by 39% (CI, 6%–61%) (5.2% vs. 8.4%; $p = 0.02$). BMD increased significantly compared with placebo at the LS (5.4% vs. 1.1%), femoral neck (1.6% vs. 21.2%), femoral trochanter (3.3% vs. 20.7%), and midshaft of the radius (0.2% vs. 21.4%). Bone biopsies obtained showed histologically normal bone.

23. (1) **Reginster J, Minne HW, Sorensen OH,** et al. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. Osteoporos Int 2000;11:83–91.

The design of this European arm of the VERT study was similar to that of the US arm. The study included 1,226 postmenopausal women. Risedronate reduced the risk of new vertebral fractures by 49% over a 3-year period compared with placebo ($p < 0.001$). A significant reduction of 61% was seen within the 1st year ($p = 0.001$). The risk of nonvertebral fractures was reduced by 33% compared with placebo over a 3-year period ($p = 0.06$). Risedronate significantly increased BMD at the spine and hip within 6 months. The adverse-event profile of risedronate was not significantly different from that with placebo.

24. (2) **Mellstrom DD, Sorensen OH, Goemaere S, Roux C, Johnson TD, Chines AA.** Seven years of treatment with risedronate in women with postmenopausal osteoporosis. Calcif Tissue Int 2004;75:462–468.

    This was the second 2-year extension of an originally 3-year, randomized, placebo-controlled trial that assessed the effect of risedronate on BMD and fractures. In this portion of the trial, 164 subjects enrolled, and 83% of them (136 subjects) completed the 2-year phase. All patients received 5 mg/d of risedronate. In those who had been receiving treatment before this extension, their BMD gains persisted or improved. The incidence of vertebral fractures remained similar in years 4 through 7. Those who were in the placebo group before this extension experienced significant BMD gains; they also noted decreases in fracture rates similar to those in the treatment group.

25. (1) **McClung MR, Geusens P, Miller PD,** et al. Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. N Engl J Med 2001;344:333–340.

    In this study, 5,445 postmenopausal women, 70 to 79 years old with osteoporosis (femoral neck *T*-score −4 or less or below −3 with a nonskeletal risk factor for hip fracture, such as poor gait or a propensity to fall; group 1) and 3,886 women at least 80 years old who had at least one nonskeletal risk factor for hip fracture or low BMD at the femoral neck (*T*-score below −4 or below −3 with a hip axis length ≤11.1 cm; group 2) were randomly assigned to receive oral risedronate (2.5 or 5.0 mg/d) or placebo for 3 years. The incidence of hip fracture among all the women in the risedronate group was reduced significantly (RR, 0.7; CI, 0.6–0.9; $p = 0.02$). In group 1, a significant reduction in hip fractures was found compared with the placebo group (RR, 0.6; CI, 0.4–0.9; $p = 0.009$). In group 2, the incidence of hip fracture was not significantly different between the two groups ($p = 0.35$).

26. (1) **Cranney A, Tugwell P, Adachi J,** et al. Meta-analyses of therapies for postmenopausal osteoporosis. III. Meta-analysis of risedronate for the treatment of postmenopausal osteoporosis. Endocr Rev 2002;23:517–523.

    This was a meta-analysis of eight randomized trials that compared risedronate with placebo. The pooled RR of vertebral fractures in postmenopausal women given 2.5 mg or more of risedronate was 0.64 (CI, 0.54–0.77). The pooled RR of nonvertebral fractures was 0.73 (CI, 0.61–0.87). Mean percentage change difference between risedronate and placebo was 4.54% (CI, 4.12–4.97) in the LS and 2.75% (CI, 2.32–3.17) in the femoral neck.

27. (2) **Watts NB, Chines A, Olszynski WP,** et al. Fracture risk remains reduced one year after discontinuation of risedronate. Osteoporos Int 2008;19:365–372.

    Postmenopausal women who were treated with risedronate for 3 years were followed for 1 year after discontinuation of risedronate. During the year off treatment, BMD of LS and femoral neck declined but remained significantly higher than baseline BMD and BMD of the placebo group. BTMs (BSAP, urinary NTX) significantly declined and were similar to the control group. However, despite these changes, the risk of new morphometric vertebral fractures was 46% lower in the former risedronate group compared to the control group.

28. (1) **Brown JP, Kendler DL, McClung MR,** et al. The efficacy and tolerability of risedronate once a week for the treatment of postmenopausal osteoporosis. Calcif Tissue Int 2002;71:103–111.

    This study's design included a randomized, double-blind, active-controlled group of 1,456 postmenopausal women 50 years and older with *T*-score of less than −2.5 or of less than −2.0 with at least one prevalent fracture. Risedronate (35 mg once weekly, 50 mg once weekly, and 5 mg once daily) had similar efficacy and safety profiles. The mean percentage change in LS BMD after 12 months was 4.0% (0.2%) in the 5-mg daily group, 3.9% (0.2%) in the 35-mg group, and 4.2% (0.2%) in the 50-mg group.

29. (1) **Delmas PD, McClung MR, Zanchetta JR,** et al. Efficacy and safety of risedronate 150 mg once a month in the treatment of postmenopausal osteoporosis. Bone 2008;42:36–42.

    Risedronate 150 mg once a month oral dose was shown to be noninferior compared to the 5 mg daily regimen administered to postmenopausal women with osteoporosis with regard to changes in hip BMD and changes in BTMs.

30. (1) **Eastell R, Devogelaer JP, Peel NF,** et al. Prevention of bone loss with risedronate in glucocorticoid-treated rheumatoid arthritis patients. Osteoporos Int 2000;11:331–337.

This was a 2-year, double-masked, placebo-controlled trial with a 3rd year of nontreatment follow-up in which 120 women on long-term glucocorticoid therapy (>2.5 mg/d prednisolone) were randomly assigned to receive daily placebo, risedronate 2.5 mg/d, or cyclic risedronate (15 mg/d for 2 of 12 weeks). At the end of 97 weeks, BMD was maintained at the LS (1.4%) and trochanter (0.4%) in the daily 2.5-mg risedronate group, whereas significant bone loss occurred in spine and hip of the placebo group (−1.6%, $p = 0.03$; and −4.0%; $p < 0.005$, respectively). At the femoral neck, an insignificant bone loss was noted in the daily 2.5-mg risedronate group (−1.0%), whereas in the placebo group, bone density decreased significantly (−3.6%; $p < 0.001$). The difference between placebo and daily 2.5-mg risedronate groups was significant at the LS ($p = 0.009$) and trochanter ($p = 0.02$) but was not significant at the femoral neck. Although not significantly different from placebo at the LS, the overall effect of the cyclic regimen was similar to that of the daily 2.5-mg risedronate regimen. After treatment was withdrawn, significant bone loss occurred at the LS. Adverse events (including upper gastrointestinal events) were similar across treatment groups.

31. (1) **Reid DM, Hughes RA, Laan RF,** et al. Efficacy and safety of daily risedronate in the treatment of corticosteroid-induced osteoporosis in men and women: a randomized trial. European Corticosteroid-Induced Osteoporosis Treatment Study. J Bone Miner Res 2000;15:1006–1013.

    This was a multicenter, double-blind, placebo-controlled study of 290 men and women taking high-dose oral corticosteroid therapy (prednisone ≤7.5 mg/d or equivalent) for less than or equal to 6 months. Risedronate, 2.5 or 5 mg/d, or placebo was administered for 12 months. All patients received 1 g calcium and 400 IU vitamin D daily. The primary end point was LS BMD at month 12. Overall, statistically significant treatment effects were found on BMD at 12 months at the LS ($p < 0.001$), femoral neck ($p = 0.004$), and trochanter ($p = 0.010$). Risedronate, 5 mg, increased BMD at 12 months by an SEM of 2.9% (0.49%) at the LS, 1.8% (0.46%) at the femoral neck, and 2.4% (0.54%) at the trochanter, whereas BMD was maintained only in the control group. The incidence of vertebral fractures was reduced by 70% in the combined risedronate treatment groups, relative to placebo ($p = 0.042$). No difference in gastrointestinal adverse events was noted between the risedronate and placebo groups.

32. (1) **Reginster JY, Wilson KM, Dumont E, Bonvoisin B, Barrett J.** Monthly oral ibandronate is well tolerated and efficacious in postmenopausal women: results from the monthly oral pilot study. J Clin Endocrinol Metab 2005;90:5018–5024.

    In this randomized, double-blind, multicenter, placebo-controlled study, 144 postmenopausal women were given 50, 100, or 150 mg of ibandronate or placebo monthly. They were followed up for 3 months for tolerability and changes in the BTM CTX. No significant differences in adverse events compared with placebo were discovered. CTX significantly decreased over these 3 months in those taking 100- and 150-mg dosages (serum, −40.7% and −56.7%, respectively, $p < 0.001$; urinary, −34.6% and −54.1%, respectively, $p < 0.001$).

33. (1) **Miller PD, McClung MR, Macovei L,** et al. Monthly oral ibandronate therapy in postmenopausal osteoporosis: 1-year results from the MOBILE study. J Bone Miner Res 2005;20:1315–1322.

    This was a randomized, double-blind trial that searched for the appropriate ibandronate dose for the treatment of osteoporosis. The 1,609 postmenopausal osteoporotic women in the study were assigned to four groups: 2.5 mg daily, 50 mg/50 mg once a month, 100 mg once a month, or 150 mg once a month, and they were followed up for 2 years. Those taking monthly ibandronate experienced increases in LS (3.9%, 4.3%, 4.1%, and 4.9%, respectively) and similar increases in hip BMD (2%–3%). The 150-mg group had small but significantly greater increases in LS BMD than did the group with the daily regimen ($p < 0.0001$). When the groups were evaluated for those who achieved BMD gains above baseline as well as greater than 6% at the LS or 3% at the hip, the 150-mg and 100-mg groups had significantly more patients at these goals than did those with the daily regimen at the LS and at the hip (only 150 mg at the LS with respect to gains above baseline). Regarding side effects, the frequency of gastrointestinal symptoms with each dose was similar, but there was a small increase in flu-like symptoms with the monthly regimens (6.6% in the 50-mg/50-mg group, 6.8% in the 100-mg group, 8.3% in the 150-mg group, and 2.8% in the daily group).

34. (2) **Felsenberg D, Czerwinski E, Stakkestad J, Neate C, Masanauskaite D, Reginster J-Y.** Efficacy of monthly oral ibandronate is maintained over 5 years: the MOBILE LTE study. Osteoporos Int 2009;20:S5–S22.

    The patients ($n = 719$) who were previously enrolled in the 2-year MOBILE (Monthly Oral iBandronate In LadiEs) study were continued on monthly ibandronate for an additional 3 years in the MOBILE LTE study. The results showed that in patients receiving 5 years of continuous monthly ibandronate (100 or 150 mg), LS BMD increased by 8.2% and 8.4%, respectively, compared with MOBILE baseline.

35. (1) **Eisman JA, Civitelli R, Adami S,** et al. Efficacy and tolerability of intravenous ibandronate injections in postmenopausal osteoporosis: 2-year results from the DIVA study. J Rheumatol 2008;35:488–497.

The DIVA study examined the optimal ibandronate IV injection dosing for treatment of postmenopausal osteoporosis by comparing the efficacy and tolerability of 2- and 3-monthly injections with the previously evaluated daily oral ibandronate regimen. This was a randomized, double-blind, double-dummy, noninferiority study of 1,395 women with osteoporosis examining the effects of 2 years of IV ibandronate (2 mg every 2 months or 3 mg every 3 months) or oral ibandronate on LS and proximal femur BMD. The results showed that at 2 years, both IV regimens achieved statistically noninferior and also superior increases in LS BMD compared with the daily regimen. The tolerability profile of the IV regimens was similar to that observed with daily oral therapy.

36. (1) **Chesnut IC, Skag A, Christiansen C,** et al. Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. J Bone Miner Res 2004;19:1241–1249.

This was a randomized, double-blind, placebo-controlled, parallel-group trial of 2,946 postmenopausal women with BMD *T*-score less than or equal to −2.0 at the LS and history of vertebral fracture treated with either placebo or ibandronate 2.5 mg/d or 20 mg every other day for 12 doses every 3 months. There was a 6.5%, 5.7%, and 1.3% increase in LS BMD in the daily ibandronate, intermittent ibandronate, and placebo groups, respectively, after 3 years of treatment. The risk of new morphometric vertebral fractures was reduced by 62% ($p = 0.0001$) and 50% ($p = 0.0006$) in the daily and intermittent ibandronate groups, respectively, compared to placebo. There was a 49% and 48% relative RR in clinical vertebral fractures in the daily and intermittent ibandronate groups, respectively.

37. (1) **Black DM, Delmas PD, Eastell R,** et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med 2007;356:1809–1822.

In this double-blind, placebo-controlled trial, 7,765 postmenopausal women with osteoporosis (based on *T*-score of <−2.5 or *T*-score of −1.5 or less with radiologic evidence of vertebral fracture) were assigned to receive a single 15-minute infusion of zoledronic acid (5 mg) or placebo at baseline, at 12 and 24 months. Treatment with zoledronic acid reduced the risk of morphometric vertebral fracture by 70% and reduced the risk of hip fracture by 41% after 3 years of treatment compared to placebo. There was also a significant improvement in BMD and BTMs in the group treated with zoledronic acid. Adverse events were similar in the two study groups.

38. (1) **Lyles KW, Colon-Emeric CS, Magaziner JS,** et al. Zoledronic acid and clinical fractures and mortality after hip fracture. N Engl J Med 2007;357:1799–1809.

In this randomized, double-blind, placebo-controlled trial, patients who were within 90 days of surgical repair of a hip fracture were randomized to receive yearly IV zoledronic acid (5 mg) or placebo. The rates of any new clinical fracture were 8.6% in the zoledronic acid group and 13.9% in the placebo group, a 35% RR with zoledronic acid. The rates of new clinical vertebral fractures and new nonvertebral fractures were also lower in the zoledronic acid group. There was a 28% reduction in all-cause mortality in the zoledronic acid group.

39. (3) **de Groen PC, Lubbe DF, Hirsch LJ,** et al. Esophagitis associated with the use of alendronate. N Engl J Med 1996;335:1016–1021.

Report of three cases of severe esophagitis among alendronate-treated patients and review of postmarketing data

40. (1) **Lanza F, Schwartz H, Sahba B,** et al. An endoscopic comparison of the effects of alendronate and risedronate on upper gastrointestinal mucosae. Am J Gastroenterol 2000;95:3112–3117.

This was a multicenter, randomized, parallel-group, double-blind, placebo-controlled trial of 235 patients (men or postmenopausal women, aged 45–80 years) with normal upper gastrointestinal endoscopies at baseline. They received 28 days of the following therapy: alendronate, 40 mg/d; risedronate, 30 mg/d; and placebo, or placebo with aspirin, 650 mg four times per day, for the last 7 days. Endoscopy was repeated on day 29. After 28 days of treatment, the alendronate and risedronate groups had comparable mean gastric and duodenal erosion scores, which were significantly lower than those of the aspirin group. Esophageal scores were comparable in all groups. Gastric ulcers alone, or combined with large numbers of gastric erosions, occurred in 3% of alendronate and risedronate patients versus 60% in those treated with aspirin and placebo.

41. (1) **Lanza FL, Hunt RH, Thomson AB, Provenza JM, Blank MA.** Endoscopic comparison of esophageal and gastroduodenal effects of risedronate and alendronate in postmenopausal women. Gastroenterology 2000;119:631–638.

Healthy postmenopausal women were randomly assigned to receive 5 mg risedronate or 10 mg alendronate for 2 weeks. Endoscopies were performed at baseline and on days 8 and 15.

Gastric ulcers were observed during the treatment period in 9 of 221 (4.1%) evaluable subjects on risedronate compared with 30 of 227 (13.2%) taking alendronate ($p < 0.001$). Mean gastric endoscopy scores for the risedronate group were lower than those for the alendronate group at days 8 and 15 ($p \geq 0.001$). Mean esophageal and duodenal endoscopy scores were similar in the two groups at days 8 and 15. Esophageal ulcers were noted in three evaluable subjects in the alendronate group, compared with none in the risedronate group, and duodenal ulcers were noted in one evaluable subject in the alendronate group and two in the risedronate group.

42. (1) **Taggart H, Bolognese MA, Lindsay R,** et al. Upper gastrointestinal tract safety of risedronate: a pooled analysis of 9 clinical trials. Mayo Clin Proc 2002;77:262–270.

The nine included studies enrolled 10,068 men and women who received placebo or 5 mg of risedronate sodium for greater than or equal to 3 years (intent-to-treat population). The treatment groups were similar with respect to baseline gastrointestinal tract disease and use of concomitant treatments during the studies. No significant difference was found in upper gastrointestinal tract adverse events in the risedronate and placebo groups (29.8% and 29.6%, respectively). Risedronate-treated patients with preexisting active upper gastrointestinal disease did not experience worsening of their underlying conditions or an increased frequency of upper gastrointestinal adverse events. Concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs), requirement for gastric antisecretory drugs, or the presence of active gastrointestinal tract disease did not result in a higher frequency of upper gastrointestinal tract adverse events in the risedronate-treated patients compared with findings in controls. Endoscopy, performed in 349 patients, demonstrated no statistically significant differences across treatment groups.

43. (3) **Ruggiero SL, Mehrotra B, Rosenberg TJ, Engroff SL.** Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. J Oral Maxillofac Surg 2004;62:527–534.

ONJ was first brought into focus by this descriptive study of 63 cases.

44. (1) **Grbic JT, Landesberg R, Lin SQ,** et al. Incidence of osteonecrosis of the jaw in women with postmenopausal osteoporosis in the health outcomes and reduced incidence with zoledronic acid once yearly pivotal fracture trial. J Am Dent Assoc 2008;139:32–40.

This study examined the incidence of ONJ (defined as exposed bone in the maxillofacial area with delayed healing for more than 6 weeks despite appropriate care) in a prospective 3-year clinical trial of zoledronic acid in postmenopausal women. Only one participant who received placebo and one participant who received zoledronic acid experienced ONJ. The study concluded that the occurrence of ONJ is rare.

45. (2) **Sorensen HT, Christensen S, Mehnert F,** et al. Use of bisphosphonates among women and risk of atrial fibrillation and flutter: population based case-control study. BMJ 2008;336:813–816.

This was a population-based, case-control study, using medical databases from Denmark to examine the relative risk of atrial fibrillation and flutter. The study examined 13,586 patients with atrial fibrillation and flutter and 68,054 population controls. The adjusted relative risk of patients who were on bisphosphonates compared with those who were not on bisphosphonates was 0.95. New users had a relative risk of 0.75. The relative risk estimates were independent of number of prescriptions. This study did not find an increased risk of atrial fibrillation and flutter in patients on bisphosphonates.

46. (4) **Shane E, Burr D, Ebeling PR,** et al. Atypical subtrochanteric and diaphyseal femoral fractures: report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res 2010;25:2267–2294.

The ASBMR task force, which consisted of a multidisciplinary expert group, issued a statement position after reviewing the data regarding atypical femur fractures and issued a statement regarding the case definition and possible contributing factors to development of atypical fractures. Based on the available data, it was concluded that the incidence of atypical femoral fractures associated with bisphosphonate therapy for osteoporosis appears to be very low, particularly compared with the number of vertebral, hip, and other fractures that are prevented by bisphosphonates. The task force also concluded that a causal association between bisphosphonate use and atypical fractures has not been established. The task force did note that the risk of atypical fractures rises with increasing duration of exposure, and there is concern that lack of awareness and underreporting may mask the true incidence of the problem. The task force recommended an international registry be established to facilitate studies of the clinical and genetic risk factors and optimal surgical and medical management of these fractures.

47. (1) **Black DM, Kelly MP, Genant HK,** et al. Bisphosphonates and fractures of the subtrochanteric or diaphyseal femur. N Engl J Med 2010;362:1761–1771.

The authors of this study performed secondary analyses using the results of three large, randomized bisphosphonate trials: the FIT, the FIT Long-Term Extension (FLEX) trial, and the HORIZON Pivotal Fracture Trial (PFT). They reviewed 284 records for hip or femur fractures

among 14,195 women. A total of 12 fractures in 10 patients were classified as occurring in the subtrochanteric or diaphyseal femur, a combined rate of 2.3 per 10,000 patient-years. The RH was 1.03 compared to placebo for alendronate use in the FIT trial, 1.50 for zoledronic acid use in the HORIZON-PFT trial, and 1.33 for continued alendronate use in the FLEX trial. The study concluded that the incidence of subtrochanteric or diaphyseal femur fractures was low; however, the study was underpowered for definitive conclusions.

48. (4) **Watts NB, Bilezikian JP, Camacho PM,** et al. American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for the diagnosis and treatment of postmenopausal osteoporosis. Endocr Pract 2010;(16 suppl 3):1–37.

49. (1) **Ettinger B, Black DM, Mitlak BH,** et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. JAMA 1999;282:637–645.

    This is a multicenter, randomized, blinded, placebo-controlled trial of 7,705 postmenopausal women with osteoporosis. They were randomly assigned to receive 60 or 120 mg/d of raloxifene or placebo. At 36 months, the risk of vertebral fracture was reduced in both study groups receiving raloxifene (60 mg/d group: RR, 0.7, and CI, 0.5–0.8; 120 mg/d group: RR, 0.5, and CI, 0.4–0.7). Frequency of vertebral fracture was reduced both in women with (50% reduction) and without prevalent fractures (30% reduction). Nonvertebral fracture reduction was not significant. Raloxifene increased BMD in the femoral neck by 2.1% (60 mg) and 2.4% (120 mg) and in the spine by 2.6% (60 mg) and 2.7% (120 mg) ($p < 0.001$ for all comparisons). Women receiving raloxifene had increased risk of venous thromboembolus compared with those taking placebo (RR, 3.1; CI, 1.5–6.2).

50. (1) **Delmas PD, Ensrud KE, Adachi JD,** et al. Efficacy of raloxifene on vertebral fracture risk reduction in postmenopausal women with osteoporosis: Four-year results from a randomized clinical trial. J Clin Endocrinol Metab 2002;87:3609–3617.

    This was a 4-year extension of the MORE trial. The 4-year cumulative RRs for one or more new vertebral fractures were 0.64 (CI, 0.53–0.76) with raloxifene, 60 mg/d, and 0.57 (CI, 0.48–0.69) with raloxifene, 120 mg/d. The nonvertebral fracture risk was not significantly reduced (RR, 0.93; CI, 0.81–1.06). The safety profile after 4 years was similar to that observed after 3 years.

51. (1) **Cranney A, Tugwell P, Zytaruk N,** et al. Meta-analyses of therapies for postmenopausal osteoporosis. IV. Meta-analysis of raloxifene for the prevention and treatment of postmenopausal osteoporosis. Endocr Rev 2002;23:524–528.

    This was a meta-analysis of seven trials comparing raloxifene with placebo. Pooled mean percentage increase in LS BMD was 2.51% (CI, 2.21–2.82), hip was 2.11 (CI, 1.68–2.53), total body was 1.33% (CI, 0.37–2.30), and forearm was 2.05% (CI, 0.71–3.39). Vertebral fracture reduction was 40% (CI, 0.5–0.7). Nonvertebral fracture reduction was not significant.

52. (1) **Siris ES, Harris ST, Eastell R,** et al. Skeletal effects of raloxifene after 8 years: results from the continuing outcomes relevant to Evista (CORE) study. J Bone Miner Res 2005;20:1514–1524.

    The CORE trial was multicenter, double-blind study that assessed the effects of raloxifene on breast cancer for 4 additional years beyond the 4-year MORE osteoporosis treatment trial. Four thousand eleven postmenopausal women from MORE either received placebo or raloxifene 60 mg/d. The secondary end point of the study was new nonvertebral fractures. The risk of at least one new nonvertebral fracture was similar in the placebo (22.9%) and raloxifene (22.8%) groups with a hazard ratio of 1.00. However, there was a decreased risk of fracture at six major nonvertebral sites in women with prevalent vertebral fractures (HR, 0.78). Bone density was significantly higher from MORE baseline at all time points at the LS and femoral neck with raloxifene.

53. (1) **Chesnut CH III, Silverman S, Andriano K,** et al. A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the prevent recurrence of osteoporotic fractures study. PROOF Study Group. Am J Med 2000;109:267–276.

    This was a 5-year, prospective, randomized, placebo-controlled study of 1,255 postmenopausal women with one or more vertebral compression fractures and with an LS T-score of −2 or lower. The incidence of new vertebral fractures decreased significantly by 33% ($p = 0.05$) only in the 200-IU calcitonin group but not the 100-IU or 400-IU dose. No significant difference was seen in nonvertebral fracture RR between placebo and calcitonin.

54. (1) **Cranney A, Tugwell P, Zytaruk N,** et al. Meta-analyses of therapies for postmenopausal osteoporosis. VI. Meta-analysis of calcitonin for the treatment of postmenopausal osteoporosis. Endocr Rev 2002;23:540–551.

In this meta-analysis of 30 studies, calcitonin reduced the incidence of vertebral fractures by 54% (CI, 0.25–0.87) over placebo. In a large randomized trial, the RR was 0.79 (CI, 0.62–1.0). The pooled RR for nonvertebral fractures was 0.52 (CI, 0.22–1.23). In the largest trial, this was not significant. Pooled increases in weighted mean difference were 3.74 (CI, 2.04–5.43) for the LS, 3.02 (CI, 0.98–5.07) at the combined mean forearm, and 3.80 ($p = 0.07$) at the femoral neck.

55. (1) **Wells G, Tugwell P, Shea B,** et al. Meta-analyses of therapies for postmenopausal osteoporosis. V. Meta-analysis of the efficacy of hormone replacement therapy in treating and preventing osteoporosis in postmenopausal women. Endocr Rev 2002;23:529–539.

This meta-analysis of 57 randomized studies showed a trend toward reduction of incidence of vertebral fractures (RR, 0.66; CI, 0.41–1.07; five trials) and nonvertebral fractures (RR, 0.87; CI, 0.71–1.08; six trials) with HRT. BMD increase was 6.76% at 2 years in the LS (21 trials), 4.12% (9 trials) in the femoral neck, and 4.53% (14 trials) in the forearm.

56. (1) **Rossouw JE, Anderson GL, Prentice RL,** et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321–333.

In this randomized control study of greater than 16,000 postmenopausal women, Prempro (a proprietary named for conjugated equine estrogen (CEE), 0.625 mg, and medroxyprogesterone 2.5 mg) significantly reduced the risk of clinical vertebral fractures by 34%, hip fractures by 34%, and all fractures by 24% over placebo over a 5-year period. Increased breast cancer and CV risk led to discontinuation of this treatment arm. Estimated hazard ratios were as follows: congestive heart disease, 1.29 (CI, 1.02–1.63); breast cancer, 1.26 (CI, 1.00–1.59); stroke, 1.41 (CI, 1.07–1.85); pulmonary embolism, 2.13 (CI, 1.39–3.25); colorectal cancer, 0.63 (CI, 0.43–0.92); endometrial cancer, 0.83 (CI, 0.47–1.47); hip fracture, 0.66 (CI, 0.45–0.98); death due to other causes, 0.92 (CI, 0.74–1.14).

57. (1) **Bone HG, Greenspan SL, McKeever C,** et al. Alendronate and estrogen effects in postmenopausal women with low bone mineral density. Alendronate/Estrogen Study Group. J Clin Endocrinol Metab 2000;85:720–726.

This was a prospective, double-blind, placebo-controlled, randomized clinical trial in which 425 postmenopausal women who had previously undergone hysterectomy with low bone mass were randomly assigned to receive placebo, oral alendronate, 10 mg/d, conjugated estrogen, 0.625 mg/d, or a combination of the two drugs. At 2 years, mean percentage changes in LS BMD were 0.6% for placebo, 6% for alendronate ($p < 0.001$ vs. placebo), 6% for CEE ($p < 0.001$ vs. placebo), and 8.3% for combination therapy ($p < 0.001$ vs. placebo and CEE; $p = 0.022$ vs. alendronate). The corresponding changes in total proximal femur BMD were 4.0%, 3.4%, 4.7%, and 0.3% for the alendronate, estrogen, alendronate plus estrogen, and placebo groups, respectively. Greater reductions in urinary NTX and BSAP were seen in the combination therapy than with either one alone.

58. (1) **Lindsay R, Cosman F, Lobo RA,** et al. Addition of alendronate to ongoing hormone replacement therapy in the treatment of osteoporosis: a randomized, controlled clinical trial. J Clin Endocrinol Metab 1999;84:3076–3081.

In this randomized, placebo-controlled trial of 428 postmenopausal women with osteoporosis who had been receiving HRT for less than or equal to 1 year, alendronate, 10 mg/d plus HRT, produced significantly greater increases in BMD of the LS (3.6% vs. 1.0%; $p < 0.001$) and hip trochanter (2.7% vs. 0.5%; $p < 0.001$) compared with HRT alone; the intergroup difference in BMD at the femoral neck was not significant (1.7% vs. 0.8%; $p = 0.072$). Serum BSAP and urine NTX decreased significantly at 6 and 12 months with alendronate plus HRT, after which they remained within premenopausal levels. No differences in upper gastrointestinal adverse events or fractures were seen.

59. (1) **Johnell O, Scheele WH, Lu Y, Reginster JY, Need AG, Seeman E.** Additive effects of raloxifene and alendronate on bone density and biochemical markers of bone remodeling in postmenopausal women with osteoporosis. J Clin Endocrinol Metab 2002;87:985–992.

This study was a phase 3, randomized, double-blind, 1-year trial that evaluated the effects of combined raloxifene and alendronate in 331 postmenopausal women with osteoporosis. Patients received placebo, raloxifene, 60 mg/d, alendronate, 10 mg/d, or a combination of the latter two. Mean LS BMD increases over baseline were 2.1%, 4.3%, and 5.3% in the raloxifene, alendronate, and combination groups, respectively ($p < 0.05$). The mean increase in femoral neck BMD in the combination group was 3.7% compared with the 2.7% and 1.7% increases in the alendronate ($p = 0.02$) and raloxifene ($p < 0.001$) groups, respectively. The changes from baseline to 12 months in bone markers ranged from −7.1% to −16.0% with placebo, −23.8% to −46.5% with raloxifene, −42.3% to −74.2% with alendronate, and −54.1% to −81.0% in the raloxifene–alendronate combination group. Although the alendronate group had changes in BMD and bone markers that were approximately twice the magnitude found in the raloxifene group, clinical correlation to fractures is not known. Combined therapy reduced markers of bone turnover to a greater degree than did either drug alone.

60. (1) **Neer RM, Arnaud CD, Zanchetta JR,** et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med 2001;344:1434–1441.

In this study, 1,637 postmenopausal women with prior vertebral fractures were randomly assigned to once-daily 20 or 40 μg SC of PTH (1-34) or placebo for a median of 21 months. RRs of fracture in the 20- and 40-μg groups, compared with placebo, were 0.35 (CI, 0.22–0.55) and 0.3 (CI, 0.19–0.50). Nonvertebral fracture RRs were 0.47 (CI, 0.25–0.88) and 0.46 (CI, 0.25–0.861). Compared with placebo, the 20-mg and 40-mg doses of PTH increased LS BMD by 9% and 13%, and by 3% and 6% in the femoral neck; the 40-mg dose decreased BMD at the shaft of the radius by 2%, but total body BMD was increased by 2% to 4%. Most common side effects included nausea and headache.

61. (2) **Prince R, Sipos A, Hossain A,** et al. Sustained nonvertebral fragility fracture risk reduction after discontinuation of teriparatide treatment. J Bone Miner Res 2005;20:1507–1513.

This observational study assessed nonvertebral changes in 1,262 of the FPT subjects for 30 months after discontinuation of teriparatide. Although the hazard ratios for nonvertebral fragility fractures remained significantly less in the treatment groups when the entire 50 weeks were analyzed, if the period after teriparatide discontinuation was solely assessed, only the 40-mg group had a significant decrease. BMD decreased after teriparatide discontinuation in both groups, except in those taking bisphosphonates for less than or equal to 2 years during the trial.

62. (2) **Lindsay R, Scheele WH, Neer R,** et al. Sustained vertebral fracture risk reduction after withdrawal of teriparatide in postmenopausal women with osteoporosis. Arch Intern Med 2004;164:2024–2030.

This is an observational study of 1,262 FPT subjects who were followed up for 18 months after teriparatide discontinuation. The treatment groups continued to have a significantly decreased risk of vertebral fractures (41% for 20 μg; $p = 0.004$; and 45% for 40 μg; $p = 0.001$). The absolute vertebral fracture RR was about 13% for both treatment groups. In addition, although LS BMD was still significantly greater in the treatment groups at the end of the follow-up study, those who used bisphosphonates for less than or equal to 1 year continued to gain BMD, whereas those not taking bisphosphonates lost BMD.

63. (1) **Finkelstein JS, Wyland JJ, Lee H,** et al. Effects of teriparatide, alendronate or both in women with postmenopausal osteoporosis. J Clin Endocrinol Metab 2010;95:1838–1845.

This was a randomized study of 93 postmenopausal women with low BMD who were randomized to receive alendronate 10 mg/d, teriparatide 40 μg/d, or both for 30 months. The LS BMD increased more in the group treated with teriparatide compared to alendronate or the combination group. A similar pattern was observed for femoral neck BMD. Bone markers increased more in the teriparatide group compared to the alendronate or combination group. The results showed that alendronate reduced the anabolic effect of teriparatide.

64. (1) **Body JJ, Gaich GA, Scheele WH,** et al. A randomized double-blind trial to compare the efficacy of teriparatide [recombinant human parathyroid hormone (1-34)] with alendronate in postmenopausal women with osteoporosis. J Clin Endocrinol Metab 2002;87:4528–4535.

In this randomized trial, 146 postmenopausal women with osteoporosis were studied for a median of 14 months. They received either 40 μg of teriparatide and a placebo tablet or 10 mg of alendronate and a placebo injection. A significantly greater increase in LS BMD was seen in the teriparatide group by the 3rd month ($p < 0.001$). At the study's end, significantly greater increases in LS, femoral neck, and total body BMD were noted in the teriparatide group. However, a significant decrease in distal one-third radius BMD occurred in the teriparatide group ($p \geq 0.05$). The teriparatide group also experienced a significant decrease in nonvertebral fracture incidence (4.1% vs. 13.7%; $p < 0.05$).

65. (2) **Ettinger B, San Martin J, Crans G, Pavo I.** Differential effects of teriparatide on BMD after treatment with raloxifene or alendronate. J Bone Miner Res 2004;19:745–751.

This is an 18-month observational study of 59 postmenopausal women, with a *T*-score of at least −2, taking 20 μg of teriparatide after 1.5 to 3 years of either alendronate or raloxifene. Those in the alendronate group started with lower BTMs. The markers in the raloxifene group tended to be higher, but the difference was not statistically significant except for BSAP, osteocalcin, and PINP at 1 month. At 3 and 6 months, those in the prior raloxifene group had significant LS BMD increases (2.1% at 3 months and 5.2% at 6 months), whereas the prior alendronate group did not. After the first 6 months, the rates of increase in both groups were similar. At 18 months, the raloxifene group had gained 10.2% in LS BMD, compared with 4.1% in the alendronate group ($p < 0.001$). At the hip during the first 6 months, BMD in the raloxifene group changed a little, whereas that in the alendronate group decreased by 1.8%. After 6 months, both groups had an 1.5% increase in hip BMD.

66. (1) **Bilezikian JP, Kurland ES.** Therapy of male osteoporosis with parathyroid hormone. Calcif Tissue Int 2001;69:248–251.

This was the first controlled, randomized, double-blind study of PTH in men with idiopathic osteoporosis. Twenty-three men, aged 30 to 64 years with *Z*-scores less than −2.0, were assigned to placebo or treatment. After 18 months, significant increases in LS BMD (13.5% ± 3%) and femoral neck BMD (2.9% ± 1.5%) were noted. The distal radius site did not change. No further increase in BMD was found in the LS, but the femoral neck continued to show gains during the 12-month extension. Markers of bone formation and resorption increased in the PTH arm, reaching a peak between 9 and 12 months of therapy and declining thereafter.

67. (1) **Finkelstein JS, Hayes A, Hunzelman JL, Wyland JJ, Lee H, Neer RM.** The effects of parathyroid hormone, alendronate, or both in men with osteoporosis. N Engl J Med 2003;349:1216–1226.

This is a randomized trial of 83 men, with an LS or femoral neck *T*-score of at least −2, that compared daily teriparatide, 40 μg, alendronate, 10 mg, and their combination over a period of 2.5 years (teriparatide was started at month 6). Significant increases in BMD at the LS (PA view, 7.9% vs. 18.1% vs. 14.8%, respectively; $p < 0.001$) and the femoral neck (3.2% vs. 9.7% [$p < 0.001$]) versus 6.2% ($p = 0.01$) in the teriparatide group were seen over those on either alendronate or the combination. The differences between the alendronate and the combination groups were not significantly different, except at the spine. Significant increases in ALP were noted in the teriparatide group ($p < 0.001$).

68. (2) **Kaufman JM, Orwoll E, Goemaere S,** et al. Teriparatide effects on vertebral fractures and bone mineral density in men with osteoporosis: treatment and discontinuation of therapy. Osteoporos Int 2005;16:510–516.

This observational study of BMD and fractures over a 30-month period, in 355 men who were exposed to 1 year of teriparatide, showed LS and hip BMD remained significantly higher in the teriparatide group than placebo ($p \geq 0.001$), even though BMDs overall decreased. Those taking bisphosphonates had an increase in spine and hip BMD, although the significant intergroup difference was lost. In those not taking bisphosphonates, the BMD decreased. A significant decrease in moderate to severe spine fractures was seen (83%; $p = 0.01$) at 18 months.

69. (1) **Cosman F, Nieves J, Zion M, Woelfert L, Luckey M, Lindsay R.** Daily and cyclic parathyroid hormone in women receiving alendronate. N Engl J Med 2005;353:566–575.

In this study, 126 women with osteoporosis on alendronate for at least 1 year were randomized to either continue therapy with alendronate plus daily subcutaneous injections of PTH (1-34), continue alendronate plus cycles of daily subcutaneous injections of PTH (1-34) administered for 3 months followed by 3 months without PTH, or alendronate alone for 15 months. The study showed a rise in bone-formation indexes for the groups treated with PTH (in the group receiving cyclical PTH, bone formation declined during cycles without PTH and increased again during cycles with PTH). LS BMD significantly increased by 6.1% and 5.4% in the continuous daily-treatment group and the cyclic-therapy group, respectively, compared to the alendronate group. There was no significant difference between PTH groups.

70. (2) **Cosman F, Nieves JW, Zion M, Barbuto N, Lindsay R.** Retreatment with teriparatide one year after the first teriparatide course in patients on continued long-term alendronate. J Bone Miner Res 2009;24:1110–1115.

In this study, 15 patients at high risk for fracture who had been treated with alendronate plus daily teriparatide and 12 who were treated with cyclical teriparatide (3 months of treatment with teriparatide followed by 3 months off teriparatide) for 15 months were recruited to receive a second course of teriparatide after being on alendronate alone for 1 year. Bone formation increased during both teriparatide courses. The LS BMD and mean spine BMD increased by 6.2% after the first daily course and 4.7% after retreatment and 4.1% after the first course of cyclic teriparatide and 4.9% after retreatment.

71. (1) **Cosman F, Lane NE, Bolognese MA,** et al. Effect of transdermal teriparatide administration on bone mineral density in postmenopausal women. J Clin Endocrinol Metab 2010;95:151–158.

This was a randomized, placebo-controlled study of 165 postmenopausal women with osteoporosis examining the safety and efficacy of transdermal teriparatide patch (doses 20, 30, or 40 μg, worn for 30 min/d) compared to placebo patch and subcutaneous administration of 20 μg/d of teriparatide for 6 months. Teriparatide transdermal patch significantly increased LS BMD and BTMs compared to placebo patch in a dose-dependent manner at 6 months. The BMD change in LS in the group who received the 40 μg/d teriparatide patch was comparable to the BMD increase in the group who received daily subcutaneous teriparatide injections.

72. (3) **Subbiah V, Madsen VS, Raymond AK, Benjamin RS, Ludwig JA.** Of mice and men: divergent risks of teriparatide-induced osteosarcoma. Osteoporos Int 2010;21:1041–1045.

There has been concern about the risk of developing osteosarcoma with teriparatide treatment based on the finding that 45% of the rats treated with high doses of this drug developed bone cancer. Given this, FDA mandated both a "black box" warning of this potential side effect and a company-sponsored postmarketing surveillance program. There has been one prior case report of osteosarcoma associated with teriparatide treatment, and this is the second case of osteosarcoma diagnosed after treatment with teriparatide.

73. (1) **Bone HG, Bolognese MA, Yuen CK,** et al. Effects of denosumab on bone mineral density and bone turnover in postmenopausal women. J Clin Endocrinol Metab 2008;93:2149–2157.

This was a 2-year, randomized, double-blind, placebo-controlled study of 332 postmenopausal women with LS BMD *T*-scores between −1.0 and −2.5 who received denosumab 60 mg subcutaneous injection every 6 months or placebo. Denosumab significantly increased LS BMD by 6. Five percent compared with a 0.6% increase in BMD in the placebo group. Denosumab also significantly increased BMD at the total hip and distal one-third radius and significantly decreased markers of bone turnover compared to placebo.

74. (1) **Cummings SR, San Martin J, McClung MR,** et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med 2009;361:756–765.

This was a randomized, placebo-controlled study that included 7,868 women with LS or total hip *T*-score of less than −2.5 but greater than −4.0 at the LS or total hip who received 60 mg of denosumab administered subcutaneously or placebo every 6 months for 36 months. Denosumab reduced the risk of new radiographic vertebral fracture by 68%, the risk of hip fracture by 40%, and the risk of nonvertebral fracture by 20%.

75. (1) **Kendler DL, Roux C, Benhamou CL,** et al. Effects of denosumab on bone mineral density and bone turnover in postmenopausal women transitioning from alendronate therapy. J Bone Miner Res 2010;25:72–81.

This was a multicenter, randomized, double-blind, double-dummy study of 504 postmenopausal women greater than or equal to 55 years of age with a BMD *T*-score of −2.0 or less and −4.0 or more on alendronate therapy for at least 6 months who were assigned to either continue weekly alendronate or receive subcutaneous denosumab 60 mg every 6 months for 12 months. In the group that received denosumab, total hip and LS BMD significantly increased compared to the group that continued alendronate. Serum CTX levels significantly decreased in the denosumab group compared to the alendronate group. Adverse events were similar between groups.

76. (1) **Brown JP, Prince RL, Deal C,** et al. Comparison of the effect of denosumab and alendronate on BMD and biochemical markers of bone turnover in postmenopausal women with low bone mass: a randomized, blinded, phase 3 trial. J Bone Miner Res 2009;24:153–161.

This was a double-blind study that compared the efficacy and safety of denosumab with alendronate in postmenopausal women. The study included 1,189 postmenopausal women with a LS or total hip *T*-score of less than or equal to −2.0 who either received denosumab 60 mg subcutaneous injections every 6 months plus oral placebo weekly or oral 70 mg alendronate weekly plus subcutaneous placebo injections every 6 months. Denosumab significantly increased total hip, femoral neck, and distal radius BMD after 12 months of treatment compared to alendronate. There was also a significantly greater reduction of BTMs in the denosumab group compared with the alendronate group. The overall safety profile was similar for both treatments.

77. (1) **Ellis GK, Bone HG, Chlebowski R,** et al. Randomized trial of denosumab in patients receiving adjuvant aromatase inhibitors for nonmetastatic breast cancer. J Clin Oncol 2008;26:4875–4882.

This was a study examining the effects of denosumab against AI–induced bone loss. Women with hormone receptor–positive nonmetastatic breast cancer and osteopenia treated with adjuvant AI therapy were stratified by duration of AI therapy (≤6 months or >6 months) were randomly assigned to receive placebo or subcutaneous denosumab 60 mg every 6 months. At 12 and 24 months, LS BMD has significantly increased by 5.5% and 7.6%, respectively, in the denosumab group versus placebo regardless of the duration of AI therapy. Increases in BMD were also seen at the total hip, femoral neck, and distal one-third radius. BTMs decreased with denosumab treatment.

78. (1) **Smith MR, Egerdie B, Hernandez Toriz N,** et al. Denosumab in men receiving androgen-deprivation therapy for prostate cancer. N Engl J Med 2009;361:745–755.

This was a double-blind, multicenter study that examined the effects of denosumab on BMD and fractures in men receiving androgen deprivation therapy for nonmetastatic prostate cancer. Patients were randomly assigned to receive subcutaneous denosumab 60 mg every 6 months or placebo for 24 months. At 24 months, BMD of the LS had increased by 5.6% in the denosumab group as compared with a loss of 1.0% in the placebo group ($p < 0.001$). There was also a significant increase in total hip, femoral neck, and distal one-third radius BMD. Patients

who received denosumab had a decreased incidence of new vertebral fractures at 36 months (1.5%, vs. 3.9% with placebo).

79. (1) **Shea B, Wells G, Cranney A,** et al. Meta-analyses of therapies for postmenopausal osteoporosis. VII. Meta-analysis of calcium supplementation for the prevention of postmenopausal osteoporosis. Endocr Rev 2002;23:552–559.

This is a meta-analysis of 15 trials comparing calcium with placebo. The pooled difference in percentage change from baseline was 2.05% for the total body BMD, 1.66% for the LS, and 1.64% for the hip in patients who received calcium. Vertebral fracture RR was 23%, and nonvertebral fracture reduction was 14%.

80. (1) **Papadimitropoulos E, Wells G,** Shea B, et al. Meta-analyses of therapies for postmenopausal osteoporosis. VIII: Meta-analysis of the efficacy of vitamin D treatment in preventing osteoporosis in postmenopausal women. Endocr Rev 2002;23:560–569.

This was a meta-analysis of 25 randomized trials of vitamin D with or without calcium versus control. The incidence of vertebral fractures was reduced (RR, 0.63; CI, 0.45–0.88; $p < 0.01$), and nonvertebral fracture incidence showed a trend toward reduction (RR, 0.77; CI, 0.57–1.04; $p = 0.09$). Hydroxylated vitamin D had a more profound effect on BMD than standard vitamin D. Total body BMD was increased by 2.06% in patients who received hydroxylated vitamin D compared with 0.4% in those who received standard vitamin D.

81. (1) **Bolland MJ, Avenell A, Baron JA,** et al. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. BMJ 2010;341:c3691.

This was a meta-analysis of 15 randomized, placebo-controlled trials of calcium supplements (≥500 mg/d, without coadministration of vitamin D) and study duration of more than 1 year. Patients who were treated with calcium had a higher risk of myocardial infarction compared to placebo.

82. (1) **Cameron ID, Venman J, Kurrle SE,** et al. Hip protectors in aged-care facilities: a randomized trial of use by individual higher-risk residents. Age Ageing 2001;30:477–481.

This was a randomized, controlled trial of 174 women who lived in nursing homes or aged-care facilities and who had two or more falls or at least one fall that required hospital admission in the previous 3 months. During follow-up, a mean of 4.6 falls per person occurred. No difference in mortality was found. Eight hip fractures occurred in the intervention group and seven in the control group (HR, 1.46; CI, 0.53–4.51). No hip fractures occurred when hip protectors were being worn as directed. Adherence was approximately 57% over the duration of the study, and hip protectors were worn at the time of 54% of falls in the intervention group.

83. (1) **Reginster JY, Seeman E, De Vernejoul MC,** et al. Strontium ranelate reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis: Treatment of Peripheral Osteoporosis (TROPOS) study. J Clin Endocrinol Metab 2005;90:2816–2822.

In this randomized, double-blind, placebo-controlled trial, 5,091 postmenopausal osteoporotic women received strontium ranelate, 2 g/d, or placebo for 5 years (main statistical analysis after 3 years). Nonvertebral fragility fractures significantly decreased by 19% ($p = 0.031$), in the strontium group at 3 years. Those who were 74 years or older and had a femoral neck *T*-score of at least −3 experienced a 36% RR reduction for hip fracture ($p = 0.046$). A significant RR reduction for vertebral fractures of 39% ($p < 0.001$) was seen in the strontium group at 3 years.

84. (2) **Reginster JY, Bruyere O, Sawicki A,** et al. Long-term treatment of postmenopausal osteoporosis with strontium ranelate: results at 8 years. Bone 2009;45:1059–1064.

This study examined the efficacy, safety, and tolerability of strontium ranelate 2 g/d over 8 years. Postmenopausal women with osteoporosis who had participated in the 5-year efficacy trials SOTI and TROPOS were invited to enter a 3-year open-label extension study. There was a significant annual increase in LS, femoral neck, and total hip throughout the 8-year period, except at the 8-year visit for femoral neck and total hip BMD. The cumulative incidences of new vertebral and nonvertebral fractures over years 6 to 8 was not significantly different compared to the cumulative incidences of the first 3 years of treatment in the original study.

85. (1) **Horwitz MJ, Tedesco MB, Gundberg C, Garcia-Ocana A, Stewart AF.** Short-term, high-dose parathyroid hormone-related protein as a skeletal anabolic agent for the treatment of postmenopausal osteoporosis. J Clin Endocrinol Metab 2003;88:569–575.

This was a 3-month, double-blind, placebo-controlled, randomized clinical trial of 16 healthy postmenopausal women with osteoporosis who were treated with either daily subcutaneous PTHrP or placebo injections. The group who received PTHrP had a 4.7% increase in LS BMD compared to placebo over 3 months of treatment. There was no significant difference between the two groups with regard to femoral neck BMD. In the PTHrp group, there was an increase in serum osteocalcin; however, there was no significant difference in other BTMs (including BSAP) between the two groups.

86. (1) **Padhi D, Jang G, Stouch B, Fang L, Posvar E.** Single-dose, placebo-controlled, randomized study of AMG 785, a sclerostin monoclonal antibody. J Bone Miner Res 2011;26:19–26.

This phase 1, randomized, double-blind, placebo-controlled study examined the safety and tolerability of subcutaneously or intravenously administered sclerostin monoclonal antibody (AMG 785) to healthy men and postmenopausal women. AMG 785 was well tolerated. There was one serious adverse event of nonspecific hepatitis in the treatment group. No deaths or study discontinuations occurred. Dose-related increases in the bone-formation markers were observed, along with a dose-related decrease in the bone-resorption marker. In addition, there was also a statistically significant increase in BMD of the LS and total hip compared with placebo on day 85.

87. (4) **Canalis E.** New treatment modalities in osteoporosis. Endocr Pract 2010;16:855–863.

Novel antiresorptive agents such as denosumab, new selective estrogen receptor modulators and CTSK inhibitors as well as novel anabolic therapies targeting Wnt/β-catenin signaling pathway are discussed.

88. (1) **Cummings SR, Ensrud K, Delmas PD,** et al. Lasofoxifene in postmenopausal women with osteoporosis. N Engl J Med 2010;362:686–696.

In this randomized trial 8,556 women with osteoporosis received once-daily lasofoxifene (at a dose of either 0.25 mg or 0.5 mg) or placebo for 5 years. Lasofoxifene at a dose of 0.5 mg/d reduced risk of vertebral and nonvertebral fractures, ER-positive breast cancer, coronary heart disease events, and stroke compared to placebo. Lasofoxifene at a dose of 0.25 mg/d reduced the risk of vertebral fracture and stroke compared to placebo. Both the lower and higher doses were associated with an increase in venous thromboembolic events compared to placebo.

89. (1) **Cummings SR, Ettinger B, Delmas PD,** et al. The effects of tibolone in older postmenopausal women. N Engl J Med 2008;359:697–708.

This was a randomized, double-blind, placebo-controlled study of 4,538 women with BMD *T*-score of −2.5 or less at the hip or spine or a *T*-score of −2.0 or less and radiologic evidence of a vertebral fracture, who received either once-daily tibolone (at a dose of 1.25 mg) or placebo for 3 years. Women treated with tibolone had a decreased risk of vertebral and nonvertebral fracture. The tibolone group also had a decreased risk of invasive breast cancer and colon cancer but an increased risk of stroke (for which the study was stopped in February 2006 at the recommendation of the data and safety monitoring board).

90. (2) **Bone HG, McClung MR, Roux C,** et al. Odanacatib, a cathepsin-K inhibitor for osteoporosis: a two-year study in postmenopausal women with low bone density. J Bone Miner Res 2010;25:937–947.

This was a 2-year trial to evaluate the safety and efficacy of weekly doses of placebo or 3, 10, 25, or 50 mg of odanacatib on BMD and bone markers in postmenopausal women with low BMD. There was a dose-related increase in BMD in the group treated with odanacatib. The group who was treated with 50-mg dose of odanacatib, LS and total hip BMD increased 5.5% and 3.2%, respectively, whereas BMD was unchanged in the placebo group. The safety and tolerability of odanacatib generally were similar in the treatment and placebo groups.

91. (2) **Eisman JA, Bone HG, Hosking DJ,** et al. Odanacatib in the treatment of postmenopausal women with low bone mineral density: three-year continued therapy and resolution of effect. J Bone Miner Res 2011;26:242–251.

A 1-year extension study showed that continued treatment with 50 mg of odanacatib for 3 years produced significant increases from baseline and from year 2 in spine BMD (7.9% and 2.3%) and total hip BMD (5.8% and 2.4%).

92. (1) **Cummings SR, Palermo L, Browner W,** et al. Monitoring osteoporosis therapy with bone densitometry: misleading changes and regression to the mean. Fracture Intervention Trial Research Group. JAMA 2000;283:1318–1321.

This article evaluated BMD data from the FIT and the MORE trials. Women with the greatest loss of BMD during the 1st year of treatment were the most likely to gain BMD during continued treatment. Among women receiving alendronate whose hip BMD decreased by greater than 4% during the 1st year, 83% (CI, 82%–84%) had increases in hip BMD during the 2nd year, with an overall mean increase of 4.7%. In contrast, those who seemed to gain less than or equal to 8% during the 1st year lost an average of 1% (CI, 0.1%–1.9%) during the next year. Similar results were observed with raloxifene.

93. (2) **Chapurlat RD, Palermo L, Ramsay P, Cummings SR.** Risk of fracture among women who lose bone density during treatment with alendronate. The Fracture Intervention Trial. Osteoporos Int 2005;16:842–848.

This observational study analyzed the 5,220 subjects in the FPT who took less than or equal to 70% of their study medication, focusing on end-of-study fracture reduction and BMD changes after 1 and 2 years of therapy. The investigators found that those who lost greater than or equal

to 4% of spine BMD after 1 year had a vertebral fracture RR of 60%. In addition, the subjects who lost greater than or equal to 4% of hip BMD after 1 year experienced a 53% vertebral fracture RR. However, the fracture benefit was not observed if spine and hip BMD were lost.

94. (2) **Siminoski K, Jiang G, Adachi JD,** et al. Accuracy of height loss during prospective monitoring for detection of incident vertebral fractures. Osteoporos Int 2005;16:403–410.

    This was an observational study of 985 osteoporotic postmenopausal women who were in the placebo group of the Vertebral Efficacy with Risedronate Therapy studies. Their heights were measured every 3 years, and spine films were taken. Height loss of greater than 2 cm in 3 years had the sensitivity for new vertebral fractures of only 36%, but a specificity of almost 94%, with a positive predictive value (PPV) for this degree of height loss of 35%, and a negative predictive value (PPV) of 92%.

Paget Disease

95. (2) **Siris ES, Chines AA, Altman RD,** et al. Risedronate in the treatment of Paget's disease of bone: an open label, multicenter study. J Bone Miner Res 1998;13:1032–1038.

    In this open-label study of 162 patients, risedronate was administered cyclically (30 mg daily for 84 days and then no treatment for 112 days), followed by a repeat of the cycle if ALP did not normalize or if it increased from its nadir by less than or equal to 25%. ALP normalized in 54% of patients after treatment (7–14 months). The mean percentage decreases in this marker after the cycles 1 and 2 were 66% and 70%, respectively.

96. (1) **Miller PD, Brown JP, Siris ES,** Hoseyni MS, Axelrod DW, Bekker PJ. A randomized, double-blind comparison of risedronate and etidronate in the treatment of Paget's disease of bone. Paget's Risedronate/Etidronate Study Group. Am J Med 1999;106:513–520.

    In a prospective, randomized, double-blind study, 123 patients were administered risedronate, 30 mg/d, or etidronate, 400 mg/d, for 6 months. After 12 months, serum ALP normalized in 73% of the patients in the risedronate group, compared with only 15% in the etidronate group ($p < 0.001$). Median time to normalize was shorter with risedronate (91 vs. >360 days; $p < 0.001$) and relapse rates at 18 months were lower (3% vs. 15%; $p < 0.05$) than placebo. Pain-reduction scores were significantly lower with risedronate.

97. (1) **Reid IR, Nicholson GC, Weinstein RS,** et al. Biochemical and radiologic improvement in Paget's disease of bone treated with alendronate: a randomized, placebo-controlled trial. Am J Med 1996;101:341–348.

    This is a double-blind, randomized trial comparing oral alendronate, 40 mg/d, and placebo over a 6-month period in 55 patients with Paget disease. NTX declined by 86% and serum ALP by 73% in patients taking alendronate but remained stable in those taking placebo ($p < 0.001$ between groups for both indices). ALP normalized in 48% of alendronate-treated patients. About 48% of these patients showed radiologic improvement in osteolysis, whereas 4% improved on placebo ($p = 0.02$). No evidence of osteomalacia was seen in 12 patients after biopsies.

98. (1) **Siris E, Weinstein RS, Altman R,** et al. Comparative study of alendronate versus etidronate for the treatment of Paget's disease of bone. J Clin Endocrinol Metab 1996;81:961–967.

    Eighty patients were randomly assigned to receive alendronate, 40 mg/d, or etidronate, 400 mg/d, for 6 months. Compared with etidronate, alendronate resulted in higher rates of normalization of ALP (61% vs. 17%, respectively) and greater reduction in ALP (79% vs. 44%, respectively). No osteomalacia was seen on bone biopsies in the alendronate groups.

99. (1) **Reid IR, Miller P, Lyles K,** et al. Comparison of a single infusion of zoledronic acid with risedronate for Paget's disease. N Engl J Med 2005;353:898–908.

    In two randomized, double-blind, active-controlled trials, subjects with Paget disease were given either one dose of 5 mg of zoledronic acid intravenously over a 15-minute period or 60 mg of risedronate for 6 months. After 6 months, more subjects taking zoledronic acid experienced a disease response (96% vs. 74%; $p < 0.001$), ALP normalized more often in the zoledronic acid group (88.6% vs. 57.9%; $p < 0.001$), the quality of life in those who received zoledronic acid was higher, and fewer patients in the zoledronic acid group had a relapse after; 6 months off therapy (1 of 113 in the zoledronic acid group vs. 21 of 82 in the risedronate group; $p < 0.001$).

100. (1) **Merlotti D, Gennari L, Martini G,** et al. Comparison of different intravenous bisphosphonate regimens for Paget's disease of bone. J Bone Miner Res 2007;22:1510–1517.

     This was a randomized study comparing the efficacy of pamidronate 30 mg, IV, for 2 consecutive days every 3 months or zoledronate 4 mg, IV for treatment of Paget bone disease over 15 months. After 6 months of treatment, 97% of patients receiving zoledronate had a therapeutic response compared with 45% of patients receiving pamidronate. Normalization of ALP was achieved in 93% of patients in the zoledronate group and in 35% of patients in the pamidronate group. Zoledronate was superior with respect to pamidronate in achieving biochemical remission, with therapeutic response maintained in most patients at 15 months.

101. (1) **Hosking D, Lyles K, Brown JP,** et al. Long-term control of bone turnover in Paget's disease with zoledronic acid and risedronate. J Bone Miner Res 2007;22:142–148.

This study compared the efficacy of zoledronic acid (5 mg given as a 15-minute IV infusion) with risedronate 30 mg daily by mouth for 60 days to maintain long-term control of Paget bone disease. Zoledronic acid restored biochemical markers of bone turnover into the reference range in the majority of patients with Paget disease, and biochemical remission was maintained at 2 years. Risedronate was less effective in controlling Paget bone disease compared to zoledronic acid.

102. (2) **Tucci JR, Bontha S.** Intravenously administered pamidronate in the treatment of Paget's disease of bone. Endocr Pract 2001;7:423–429.

This was a prospective nonrandomized study and review of literature in which 80 patients (52 women and 28 men; age range, 53–93 years; mean age, 76 years) were treated with a total of 180 mg of IV pamidronate over a 6- or 3-week period. The mean serum ALP level was 1,051 U/l before therapy and 386 U/l after treatment, a decrease of 63% ($p < 0.0001$). In 50 patients, the serum ALP level declined to normal range. Normalization was noted in 43 of 50 patients (86%) whose baseline ALP was less than three times the upper limit of normal, in 5 of 13 patients (38%) whose baseline ALP was three to six times the upper limit of normal, and in only 2 of 17 patients (12%) whose baseline ALP exceeded six times the upper limit of normal. Adverse events included hypocalcemia and flu-like symptoms.

Primary Hyperparathyroidism

103. (4) **Habib Z, Camacho P.** Primary hyperparathyroidism. Expert Rev Endocrinol Metab 2010;5:375–387.

An article that reviews the epidemiology, pathophysiology, possible etiologies, clinical presentation, and recommended approaches to diagnosis and management of PHPT.

104. (4) **Silverberg SJ, Lewiecki EM, Mosekilde L, Peacock M, Rubin MR.** Presentation of asymptomatic primary hyperparathyroidism: proceedings of the third international workshop. J Clin Endocrinol Metab 2009;94:351–365.

This review from the Third International Workshop on PHPT summarizes the available evidence on CV and neuropsychological manifestations and skeletal and renal sequelae of primary hyperparathyroidism.

105. (2) **Lowe H, McMahon DJ, Rubin MR, Bilezikian JP, Silverberg SJ.** Normocalcemic primary hyperparathyroidism: further characterization of a new clinical phenotype. J Clin Endocrinol Metab 2007;92:3001–3005.

This was a longintudinal cohort study where 37 patients with normocalcemic PHPT were followed for development of manifestations of the disease. A significant proportion of patients had skeletal manifestations at the time of initial diagnosis, and 40% of patients develped further signs of hyperparathyroidism after a median of 3 years of follow-up.

106. (2) **Grey A, Lucas J, Horne A, Gamble G, Davidson JS, Reid IR.** Vitamin D repletion in patients with primary hyperparathyroidism and coexistent vitamin D insufficiency. J Clin Endocrinol Metab 2005;90:2122–2126.

Twenty-one patients with PHPT and hypercalcemia of less than 12 mg/dl with vitamin D insufficiency (<20 ng/ml) were given cholecalciferol, 50,000 IU weekly, for 1 month and then monthly for 1 year. With 25(OH)D replacement to levels greater than 20 ng/ml, mean calcium and phosphate levels did not change. Calcium did not increase to greater than 12 mg/dl during the study. PTH levels significantly decreased as early as 6 months (24%; $p < 0.01$, at 6 months; 26%, $p < 0.01$ at 12 months). Of note, two patients did develop hypercalciuria.

107. (4) **Bilezikian JP, Khan AA, Potts JT, Jr.** Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the third international workshop. J Clin Endocrinol Metab 2009;94:335–339.

Summary of the recommendations from the Third International Workshop for management of asymptomatic PHPT

108. (2) **Silverberg SJ, Shane E, Jacobs TP, Siris E, Bilezikian JP.** A 10-year prospective study of primary hyperparathyroidism with or without parathyroid surgery. N Engl J Med 1999;341:1249–1255.

One hundred twenty-one patients with PHPT were followed up for 10 years. Fifty-two patients did not undergo surgery; worsening hypercalcemia, hypercalciuria, or bone loss was noted in these patients. In 14 of 52, however, indications developed for surgery, and they had to undergo parathyroidectomy.

109. (2) **Rubin MR, Bilezikian JP, McMahon DJ,** et al. The natural history of primary hyperparathyroidism with or without parathyroid surgery after 15 years. J Clin Endocrinol Metab 2008;93:3462–3470.

In this 15-year prospective cohort study, 116 patients with asymptomatic PHPT were followed after or without parathyroidectomy. Whereas patients who underwent surgery had improvement in their biochemical profiles and bone mineral densities, 37% of asymptomatic patients who were followed without surgery eventually developed indications for parathyroidectomy. Loss in cortical BMD (around 35% in the distal radius) was noted in those patients observed for 15 years.

110. (4) **Udelsman R, Pasieka JL, Sturgeon C, Young JE, Clark OH.** Surgery for asymptomatic primary hyperparathyroidism: proceedings of the third international workshop. J Clin Endocrinol Metab 2009;94:366–372.

A review of the evidence and summary of the proceedings of the Third International Workshop regarding surgery in the management of asymptomatic PHPT

111. (2) **Scholz DA, Purnell DC.** Asymptomatic primary hyperparathyroidism. 10-year prospective study. Mayo Clin Proc 1981;56:473–478.

Ten-year prospective study of patients with asymptomatic PHPT followed up at Mayo Clinic. The study was unable to come up with criteria that would predict need for surgery.

112. (2) **Rao DS, Wilson RJ, Kleerekoper M, Parfitt AM.** Lack of biochemical progression or continuation of accelerated bone loss in mild asymptomatic primary hyperparathyroidism: evidence for biphasic disease course. J Clin Endocrinol Metab 1988;67:1294–1298.

One hundred seventy-seven patients with mild asymptomatic PHPT were followed up for greater than 10 years for disease progression. No changes in biochemical progression or bone loss based on forearm BMD were noted.

113. (1) **Chow CC, Chan WB, Li JK,** et al. Oral alendronate increases bone mineral density in postmenopausal women with primary hyperparathyroidism. J Clin Endocrinol Metab 2003;88:581–587.

In a study of 40 postmenopausal women with PHPT, alendronate treatment for 48 weeks resulted in increased BMD and a decrease in BTMs compared to placebo. BTMs increased at 24 weeks after alendronate withdrawal.

114. (1) **Khan AA, Bilezikian JP, Kung A, Dubois SJ, Standish TI, Syed ZA.** Alendronate therapy in men with primary hyperparathyroidism. Endocr Pract 2009;15:705–713.

In this study, nine men with PHPT who were treated with alendronate over 2 years had an increase in BMD and a decrease in BTMs compared to six men with PHPT who received placebo.

115. (1) **Khan AA, Bilezikian JP, Kung AW,** et al. Alendronate in primary hyperparathyroidism: a double-blind, randomized, placebo-controlled trial. J Clin Endocrinol Metab 2004;89:3319–3325.

This was a randomized, placebo-controlled trial of 44 patients with PHPT, taking 10 mg alendronate or placebo daily for 1 year, and then all taking alendronate, 10 mg, for the 2nd year. The alendronate group experienced significant increases in BMD at the LS compared with placebo throughout the 2 years of the trial (6.85%; $p < 0.001$). BMD also significantly increased by 4.01% at the hip in the alendronate group ($p < 0.001$) at 12 months. BMD gains were seen at the femoral neck after 2 years (3.67%; $p = 0.038$). No significant change was noted in the treatment group at the distal one-third radius. BTMs NTX and BSAP declined by 66% at 3 months and 49% at 6 months, respectively. The calcium, PTH, and urine calcium concentrations remained stable.

116. (2) **Parker CR, Blackwell PJ, Fairbairn KJ, Hosking DJ.** Alendronate in the treatment of primary hyperparathyroid-related osteoporosis: a 2-year study. J Clin Endocrinol Metab 2002;87:4482–4489.

In 32 patients with PHPT, alendronate therapy for 24 months was associated with an increase in BMD at all sites, whereas untreated patients had bone loss at the femoral neck and the radius.

117. (1) **Rossini M, Gatti D, Isaia G, Sartori L, Braga V, Adami S.** Effects of oral alendronate in elderly patients with osteoporosis and mild primary hyperparathyroidism. J Bone Miner Res 2001;16:113–119.

In a pilot-controlled study, 26 patients aged 67 to 81 years were randomly assigned to oral 10 mg alendronate on alternate-day treatment or no treatment for 2 years. Urine deoxypyridinoline excretion significantly decreased after 1 month of alendronate, and ALP and osteocalcin, after 3 months. After 2 years, the alendronate group had significant increases in BMD at LS, total hip, and total body (+8.6% ±3.0%, +4.8% ±3.9%, and +1.2% ±1.4%) in comparison with patients at baseline and controls. Serum calcium, serum phosphate, and urinary calcium excretion significantly decreased during the first 3 to 6 months but increased to baseline afterward. Serum PTH level increased significantly during the 1st year of treatment.

118. (1) **Sankaran S, Gamble G, Bolland M, Reid IR, Grey A.** Skeletal effects of interventions in mild primary hyperparathyroidism: a meta-analysis. J Clin Endocrinol Metab 2010;95:1653–1662.

This meta-analysis compared the effects of parathyroidectomy, antiresorptive therapy, and no intervention on BMD in patients with mild PHPT. Forty publications were included, and the results show that there was a similar increase in BMD in patients treated with surgery or antiresorptive therapies, whereas untreated patients had a small (0.6%–1.0% per year) but significant loss in BMD, which persisted, but was of smaller magnitude beyond 2 years of follow-up.

119. (1) **Shoback DM, Bilezikian JP, Turner SA, McCary LC, Guo MD, Peacock M.** The calcimimetic cinacalcet normalizes serum calcium in subjects with primary hyperparathyroidism. J Clin Endocrinol Metab 2003;88:5644–5649.

This is a randomized, double-blind, placebo-controlled study, where 22 patients with PHPT received cinacalcet or placebo for 15 days and were observed for an additional 7 days. Cinacalcet therapy resulted in a decrease in serum calcium and PTH levels, without an increase in 24-hour urine calcium.

120. (1) **Peacock M, Bilezikian JP, Klassen PS, Guo MD, Turner SA, Shoback D.** Cinacalcet hydrochloride maintains long-term normocalcemia in patients with primary hyperparathyroidism. J Clin Endocrinol Metab 2005;90:135–141.

In this multicenter, randomized, double-blind, placebo-controlled trial, cinacalcet 30 mg twice daily reduced serum calcium by at least 0.5 mg/dl in 73% of patients with mild PHPT compared to placebo, along with decreasing PTH levels. The mean calcium levels in the treatment group decreased to normal within 2 weeks of therapy initiation. No changes in BMD were noted in cinacalcet-treated patients, but there was an increase in BTMs in this group.

121. (2) **Peacock M, Bolognese MA, Borofsky M,** et al. Cinacalcet treatment of primary hyperparathyroidism: biochemical and bone densitometric outcomes in a five-year study. J Clin Endocrinol Metab 2009;94:4860–4867.

In this multicenter, 4.5-year, open-label extension study, all patients were treated with cinacalcet. Patients from the original placebo group achieved a similar reduction in their calcium levels compared to the original cinacalcet group, and their serum calcium normalized within 1 month after cinacalcet initiation. All subjects subsequently maintained a normal serum calcium throughout the study duration. PTH levels also showed a sustained decrease throughout the study duration but did not normalize. Serum ALP increased with cinacalcet treatment and remained elevated but within the normal reference range. There was no significant change in BMD after cinacalcet treatment, but there was a trend toward increased *Z*-scores.

122. (2) **Marcocci C, Chanson P, Shoback D,** et al. Cinacalcet reduces serum calcium concentrations in patients with intractable primary hyperparathyroidism. J Clin Endocrinol Metab 2009;94:2766–2772.

In this open-label, single-arm trial, cinacalcet was given to 17 patients with persistent PHPT after surgical intervention or patients with PHPT who were not surgical candidates. Cinacalcet reduced serum calcium by 1 mg/dl or more in 88% of patients, but PTH levels were highly variable. There was no significant change in BTMs, and BMD was not reported.

123. (2) **Peacock M, Bilezikian JP, Bolognese MA,** et al. Cinacalcet HCl reduces hypercalcemia in primary hyperparathyroidism across a wide spectrum of disease severity. J Clin Endocrinol Metab 2010;96:E9–E18.

A pooled analysis of data from three clinical trials on cinacalcet shows that this drug is effective in reducing calcium and PTH levels regardless of disease severity.

124. (4) Sensipar Prescribing Information. http://wwwaccessdatafdagov/drugsatfda_docs/label/2011/021688s015lblpdf;Accessed 05/04/2011.

Prescribing information for Sensipar from the FDA website, with the 2011 change in indications that now include severe hypercalcemia in patients with PHPT who are unable to undergo parathyroidectomy

Parathyroid Carcinoma

125. (4) **Marcocci C, Cetani F, Rubin MR, Silverberg SJ, Pinchera A, Bilezikian JP.** Parathyroid carcinoma. J Bone Miner Res 2008;23:1869–1880.

A review article on the epidemiology, pathophysiology, clinical presentation, natural history, and management of parathyroid carcinoma

126. (4) **Dudney WC, Bodenner D, Stack BC, Jr.** Parathyroid carcinoma. Otolaryngol Clin North Am 2010;43:441–453, xi.

A case series and literature review on parathyroid carcinoma

127. (2) **Silverberg SJ, Rubin MR, Faiman C,** et al. Cinacalcet hydrochloride reduces the serum calcium concentration in inoperable parathyroid carcinoma. J Clin Endocrinol Metab 2007;92:3803–3808.

In this open-label, single-arm study of 29 patients with inoperable parathyroid carcinoma, cinacalcet reduced serum calcium level by at least 1 mg/dl in 62% of patients. Mean serum calcium decreased from 15.0 to 11.2 mg/dl in these patients. The decrease in PTH levels was not significant.

128. (4) **Barman Balfour JA, Scott LJ.** Cinacalcet hydrochloride. Drugs 2005;65:271–281.

An excellent review of the pharmacodynamics, pharmacokinetics, tolerability, dosage, and efficacy of cinacalcet. It includes descriptions of trials that have evaluated this medication.

Hypercalcemia

129. (1) **Major P, Lortholary A, Hon J,** et al. Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: a pooled analysis of two randomized, controlled clinical trials. J Clin Oncol 2001;19:558–567.

Two identical, concurrent, parallel, multicenter, randomized, double-blind, and double-dummy trials compared the efficacy and safety of zoledronic acid and pamidronate for treating hypercalcemia of malignancy. The 275 study patients had moderate to severe hypercalcemia, with a corrected serum calcium of less than or equal to 3.0 mmol/l (12.0 mg/dl). They were treated with a 5-minute infusion of zoledronic acid (4 or 8 mg) or a 2-hour infusion of pamidronate (90 mg). The response rates by day 10 for zoledronic acid, 4 and 8 mg, and pamidronate, 90 mg, were 88.4% ($p = 0.002$), 86.7% ($p = 0.015$), and 69.7%, respectively. Serum calcium normalized by day 4 in 50% of the patients treated with zoledronic acid and 33.3% of the pamidronate-treated patients. The median duration of normocalcemia was higher for zoledronic acid, 4 and 8 mg, than for pamidronate, 90 mg, with response durations of 32, 43, and 18 days, respectively.

130. (1) **Purohit OP, Radstone CR, Anthony C, Kanis JA, Coleman RE.** A randomised double-blind comparison of intravenous pamidronate and clodronate in the hypercalcaemia of malignancy. Br J Cancer 1995;72:1289–1293.

This was a prospective, randomized, double-blind study in which 41 patients with hypercalcemia of malignancy received either pamidronate, 90 mg, intravenously or clodronate, 1,500 mg, intravenously. After a median time of 4 days, 100% of patients taking pamidronate achieved normocalcemia compared with 80% who received clodronate. Normocalcemia persisted for a median for 28 days after pamidronate and 14 days after clodronate ($p < 0.01$).

131. (1) **Wimalawansa SJ.** Optimal frequency of administration of pamidronate in patients with hypercalcaemia of malignancy. Clin Endocrinol (Oxf) 1994;41:591–595.

In this prospective, randomized study, 34 patients with hypercalcemia of malignancy received IV pamidronate every 14th or 21st day for 16 weeks. Normocalcemia was achieved at 48 hours and maintained for an average of 15 days. When the drug was administered every 3 weeks, recurrent hypercalcemia was seen in 50% of patients during the 3rd week. The incidence of symptomatic hypercalcemia was significantly decreased (10%, eight separate episodes; $p < 0.01$), and survival was improved ($p < 0.05$) in patients who received pamidronate every 2nd week.

132. (1) **Ostenstad B, Andersen OK.** Disodium pamidronate versus mithramycin in the management of tumour-associated hypercalcemia. Acta Oncol 1992;31:861–864.

In this prospective, randomized study, 28 consecutive hypercalcemic patients with cancer were randomly assigned to receive pamidronate (30, 60, or 90 mg, depending on the serum calcium) or rehydration, mithramycin (repeatedly), and supportive care. Pamidronate rnormalized serum calcium in all patients, and 12 of 14 were still normocalcemic on day 12. In contrast, mithramycin was effective in only 3 of 11 patients, and in those patients, hypercalcemia recurred rapidly.

133. (4) **Guise TA, Brufsky A, Coleman RE.** Understanding and optimizing bone health in breast cancer. Curr Med Res Opin 2010;26(suppl 3):3–20.

A review on novel therapies to treat skeletal complications of cancer

134. (1) **Goodman WG, Hladik GA, Turner SA,** et al. The Calcimimetic agent AMG 073 lowers plasma parathyroid hormone levels in hemodialysis patients with secondary hyperparathyroidism. J Am Soc Nephrol 2002;13:1017–1024.

In this randomized, placebo-controlled study, 52 hemodialysis patients with secondary hyperparathyroidism were given AMG 073 as single oral doses ranging from 5 to 100 mg, or placebo. Plasma PTH levels decreased 2 hours after 25-, 50-, 75-, or 100-mg doses, decreasing by a maximum of 43% ±29%, 40% ±36%, 54% ±28%, or 55% ±39%, respectively. Plasma PTH levels decreased in all patients given doses of less than or equal to 25 mg but did not change in those who received placebo. Plasma PTH levels declined for the first 3 to 4 days and remained below baseline values after 8 days of treatment in patients who received 25- or 50-mg AMG 073. Serum calcium concentrations also decreased by 5% to 10% from pretreatment levels on 50 mg of AMG 073 for 8 days, but values were unchanged in those who received lower doses.

135. (2) **Falzon M, Zong J.** The noncalcemic vitamin D analogs EB1089 and 22-oxacalcitriol suppress serum-induced parathyroid hormone-related peptide gene expression in a lung cancer cell line. Endocrinology 1998;139:1046–1053.

This study aimed to determine whether 1,25(OH)2D3 and two nonhypercalcemic analogues, EB1089 and 22-oxa-1,25(OH)2D3 (22-oxacalcitrol [OCT]), suppress serum and epidermal growth factor–induced PTHrP gene expression in a human lung squamous cancer cell line, NCI H520. EB1089 and OCT suppressed the basal and the growth factor–stimulated levels of PTHrP in a cancer cell line associated with hypercalcemia.

Hypocalcemia

136. (3) **Pearce SH, Williamson C, Kifor O,** et al. A familial syndrome of hypocalcemia with hypercalciuria due to mutations in the calcium-sensing receptor. N Engl J Med 1996;335:1115–1122.

Six kindreds with hypoparathyroidism and hypercalciuria that worsened with vitamin D supplementation were found to have mutations in the calcium-sensing receptor gene. Five heterozygous missense mutations were detected (Asn118Lys, Phe128Leu, Thr151Met, Glu191Lys, and Phe612Ser).

137. (2) **Heaney RP, Barger-Lux MJ, Dowell MS, Chen TC, Holick MF.** Calcium absorptive effects of vitamin D and its major metabolites. J Clin Endocrinol Metab 1997;82:4111–4116.

Healthy adult males were given graded doses of vitamin D_3, 25(OH)D, and 1,25(OH)2D for 8, 4, and 2 weeks, respectively. All three vitamin D compounds significantly elevated 45Ca absorption from a 300-mg calcium load. In addition, 1,25(OH)2D was active even at the lowest dose (0.5 mg/d); 25(OH)D was also active in elevating absorption and did so without increasing total 1,25(OH)2D levels. Per the dose–response curves for 1,25(OH)2D and 25(OH)D, the potency of these two is 100:1. The absorptive effect of vitamin D_3 was seen only at the highest dose level (1,250 mg, or 50,000 IU/d) and was apparently mediated by conversion to 25(OH)D.

138. (1) **Winer KK, Ko CW, Reynolds JC,** et al. Long-term treatment of hypoparathyroidism: a randomized controlled study comparing parathyroid hormone-(1-34) versus calcitriol and calcium. J Clin Endocrinol Metab 2003;88:4214–4220.

In this 3-year, randomized, open-label trial, 27 patients with hypoparathyroidism were given either PTH twice a day or calcitriol and calcium. The patients taking PTH required 37 μg, and those taking calcitriol, approximately 0.91 μg, to attain normal calcium concentrations. Those in each therapy group did not have different calcium, phosphorus, and magnesium levels. PTH normalized urine calcium levels, whereas calcitriol did not. No significant changes were seen in BMD in the groups. The BTMs ALP, osteocalcin, urinary deoxypyridinoline, and pyridinoline excretion increased more in the PTH group ($p < 0.001$).

Osteomalacia

139. (2) **Chapuy MC, Preziosi P, Maamer M,** et al. Prevalence of vitamin D insufficiency in an adult normal population. Osteoporos Int 1997;7:439–443.

This was an observational study of 1,569 French adults between November and April. Fourteen percent had 25(OH)D concentrations greater than or equal to 12 ng/ml, and seventy-five percent had levels less than 31 ng/ml. Vitamin D concentrations varied with location. A negative association between PTH and 25(OH)D was found, and 25(OH)D levels greater than or equal to 31 ng/ml were associated with the initiation of an increase in PTH.

140. (2) **Holick MF, Siris ES, Binkley N,** et al. Prevalence of Vitamin D inadequacy among postmenopausal North American women receiving osteoporosis therapy. J Clin Endocrinol Metab 2005;90:3215–3224.

In this study, 1,536 nonhospitalized postmenopausal osteoporotic women were observed for vitamin D insufficiency risks. 25(OH)D concentrations less than 30 ng/ml were found in 52%, and less than 20 ng/ml in 18%. Decreased 25(OH)D levels were more frequent in women taking less than 400 U of vitamin D daily (25(OH)D <30 ng/ml in 63% taking <400 U/d and in 45% taking ≤400 U). 25(OH)D and PTH exhibited a negative association.

141. (4) **Heaney RP.** Functional indices of vitamin D status and ramifications of vitamin D deficiency. Am J Clin Nutr 2004;80:1706S–1709S.

Review of vitamin D, its role in disease, its measurement, and suboptimal levels

142. (3) **Fujita T, Nomura M, Okajima S, Furuya H.** Adult-onset vitamin D-resistant osteomalacia with the unresponsiveness to parathyroid hormone. J Clin Endocrinol Metab 1980;50:927–931.

A case report of a 50-year-old man with vitamin D–resistant osteomalacia

143. (3) **Itoi E, Sakurai M, Honma T, Sato K, Kasama F.** Adult-onset vitamin D-resistant osteomalacia. A case with seventeen-year follow-up. J Bone Joint Surg Am 1991;73: 932–937.

Case report of prolonged follow-up of a patient with adult-onset vitamin D–resistant osteomalacia

144. (3) **Nelson AE, Bligh RC, Mirams M,** et al. Clinical case seminar: Fibroblast growth factor 23: a new clinical marker for oncogenic osteomalacia. J Clin Endocrinol Metab 2003;88:4088–4094.

This is a case report of a patient with oncogenic osteomalacia and of the correlation found between this disease and FGF 23. The causative tumor stained for the FGF 23 mRNA and protein, and this patient's serum concentration of FGF 23 was elevated before resection of the mass, subsequently normalizing after its resection.

145. (2) **Jonsson KB, Zahradnik R, Larsson T,** et al. Fibroblast growth factor 23 in oncogenic osteomalacia and X-linked hypophosphatemia. N Engl J Med 2003;348:1656–1663.

This observational study demonstrated increased concentrations of FGF 23 in patients with oncogenic osteomalacia, which returned to normal after removal of the tumor.

146. (3) **Peterson NR, Summerlin DJ, Cordes SR.** Multiple phosphaturic mesenchymal tumors associated with oncogenic osteomalacia: case report and review of the literature. Ear Nose Throat J 2010;89:E11–E15.

A case report and discussion on oncogenic osteomalacia

147. (3) **Leicht E, Biro G, Langer HJ.** Tumor-induced osteomalacia: pre- and postoperative biochemical findings. Horm Metab Res 1990;22:640–643.

A case report of a patient who was successfully treated with surgical resection of the tumor, calcitriol, and phosphorus

148. (3) **Shane E, Parisien M, Henderson JE,** et al. Tumor-induced osteomalacia: clinical and basic studies. J Bone Miner Res 1997;12:1502–1511.

A case report of tumor-induced osteomalacia with biochemical and histologic evaluation and follow-up

149. (3) **Malhotra G, Agrawal A, Jambhekar NA,** et al. Interesting image. The search for primary tumor in a patient with oncogenic osteomalacia: F-18 FDG PET resolves the conundrum. Clin Nucl Med 2010;35:896–898.

A case report on the use of F-18 FDG PET in localizing the primary tumor in a patient with oncogenic osteomalacia

150. (3) **Tebben P, et al.** Whole-body 99mTc-sestamibi scintigraphy to localize tumors causing oncogenic osteomalacia. An abstract presented at the AACE Annual Session, 2005, Washington, DC 2005.

This is a case report of three patients with oncogenic osteomalacia, in which whole-body ^{99m}Tc sestamibi scans localized the causative tumors.

151. (1) **Carpenter TO, Keller M, Schwartz D,** et al. 24,25 Dihydroxyvitamin D supplementation corrects hyperparathyroidism and improves skeletal abnormalities in X-linked hypophosphatemic rickets—A clinical research center study. J Clin Endocrinol Metab 1996;81:2381–2388.

This prospective, 1-year, placebo-controlled trial compared 24,25(OH)2D3 supplementation with standard treatment in 15 patients with X-linked hypophosphatemia. In nine patients, 24,25(OH)2D3 normalized PTH values (peak PTH was 46.5 ± 6.6 pmol/l at entry, 42.3 ± 5.9 pmol/l after placebo, and 23.3 ± 5.4 pmol/l after 24,25(OH)2D3). Nephrogenous cyclic adenosine monophosphate decreased at night, coincident with the decrease in PTH, and serum phosphorus level was slightly higher with 24,25(OH)2D3. Radiographic features of rickets improved during 24,25(OH)2D3 supplementation in children, and osteoid surface decreased in adults.

152. (1) **Seikaly MG, Brown R, Baum M.** The effect of recombinant human growth hormone in children with X-linked hypophosphatemia. Pediatrics 1997;100:879–884.

A randomized, double-blind, crossover study was performed throughout a 24-month period in five children with X-linked hypophosphatemia. Results indicated that growth hormone therapy improved the height SD score (Z score) from a baseline of −2.66 ± 0.21 to −2.02 ± 0.25 and to −1.46 ± 0.28, after 3 and 12 months, respectively. The growth velocity SD score was −1.90 ± 0.40 in the placebo group and +4.04 ± 1.50 in the treated group. An increase in serum phosphate from 0.88 ± 0.07 mmol/l to 1.17 ± 0.14 mmol/l and tubular maximum for phosphate reabsorption (TmP/glomerular filtration rate (GFR)) from 2.12 ± 0.15 to 3.41 ± 0.25 mg/dl was observed after 3 months of rhGH therapy. However, both serum phosphate and TmP/GFR were unchanged from baseline after 6, 9, and 12 months of therapy.

153. (2) **Verge CF, Lam A, Simpson JM, Cowell CT, Howard NJ, Silink M.** Effects of therapy in X-linked hypophosphatemic rickets. N Engl J Med 1991;325:1843–1848.

Twenty-four patients with X-linked hypophosphatemic rickets (9 boys and 15 girls), aged 1 to 16 years (median, 5.3 years), were observed for 0.3 to 11.8 years (median, 3.0 years). Patients treated for less than or equal to 2 years before the onset of puberty ($n = 19$) had a mean height SD score of −1.08 compared with −2.05 in the untreated historic controls. The 13 patients who were treated with calcitriol and phosphate for less than or equal to 2 years had an increase in the mean height SD score of 0.33 (CI, 0–0.67; $p = 0.05$). Nineteen of twenty-four patients (79%) had nephrocalcinosis on renal ultrasonography. The grade of nephrocalcinosis was significantly correlated with the mean phosphate dose ($r = 0.60$; $p = 0.002$) but not with the dosage of vitamin D or the duration of therapy.

154. (3) **Weinstein RS, Whyte MP.** Heterogeneity of adult hypophosphatasia. Report of severe and mild cases. Arch Intern Med 1981;141:727–731.

Two cases with varying clinical presentations were presented.

155. (3) **Camacho PM, Painter S, Kadanoff R.** Treatment of adult hypophosphatasia with teriparatide. Endocr Pract 2008;14:204–208.

A case report of the use of teriparatide in adult hypophosphatasia

156. (3) **Gagnon C, Sims NA, Mumm S,** et al. Lack of sustained response to teriparatide in a patient with adult hypophosphatasia. J Clin Endocrinol Metab 2010;95:1007–1012.

A case report of the use of teriparatide in adult hypophosphatasia

157. (3) **Schalin-Jantti C, Mornet E, Lamminen A, Valimaki MJ.** Parathyroid hormone treatment improves pain and fracture healing in adult hypophosphatasia. J Clin Endocrinol Metab 2010;95:5174–5179.

A case report of the use of teriparatide in adult hypophosphatasia

158. (3) **Whyte MP, Mumm S, Deal C.** Adult hypophosphatasia treated with teriparatide. J Clin Endocrinol Metab 2007;92:1203–1208.

A case report of the use of teriparatide in adult hypophosphatasia

Vitamin D Deficiency

159. (4) **Holick MF. Vitamin D deficiency.** N Engl J Med 2007;357:266–281.

A comprehensive review on vitamin D deficiency, including epidemiology, complications, and therapy

160. (3) **Kumar J, Muntner P, Kaskel FJ, Hailpern SM, Melamed ML.** Prevalence and associations of 25-hydroxyvitamin D deficiency in US children: NHANES 2001–2004. Pediatrics 2009;124:e362–e370.

Data from the NHANES survery show that 61% of US children and adolescents have vitamin D insufficiency. Risk factors included older age, female gender, non-Hispanic black or Mexican-American ethnicity, obesity, poor milk intake, and excessive use of television, video, or computers. Individuals with lower vitamin D levels had higher systolic blood pressures and lower high-density lipoprotein (HDL) levels.

161. (2) **Tangpricha V, Pearce EN, Chen TC, Holick MF.** Vitamin D insufficiency among free-living healthy young adults. Am J Med 2002;112:659–662.

In a study of healthy young adults, 36% were found to have vitamin D deficiency after the winter season.

162. (3) **Thomas MK, Lloyd-Jones DM, Thadhani RI,** et al. Hypovitaminosis D in medical inpatients. N Engl J Med 1998;338:777–783.

Of 290 consecutive patients admitted to a general medicine ward, 57% had 25(OH)D levels greater than or equal to 15 ng/ml, and of these patients, 28% had levels less than 8 ng/ml. This included 43% of the patients who consumed more than the RDA of vitamin D.

163. (3) **Weng FL, Shults J, Leonard MB, Stallings VA, Zemel BS.** Risk factors for low serum 25-hydroxyvitamin D concentrations in otherwise healthy children and adolescents. Am J Clin Nutr 2007;86:150–158.

In this cross-sectional observation study in 382 healthy US children and adolescents, older age, black race, winter season, and low vitamin D intake correlated with low vitamin D levels.

164. (3) **Looker AC, Pfeiffer CM, Lacher DA, Schleicher RL, Picciano MF, Yetley EA.** Serum 25-hydroxyvitamin D status of the US population: 1988–1994 compared with 2000–2004. Am J Clin Nutr 2008;88:1519–1527.

In this study comparing two NHANES populations, 25-hydroxyvitamin D levels were lower in 2000 to 2004 compared to 1988 to 1994. In a study subgroup, higher BMI, lower milk consumption, and sun protection were associated with decreasing vitamin D levels.

165. (4) **Holick MF.** Vitamin D: importance in the prevention of cancers, type 1 diabetes, heart disease, and osteoporosis. Am J Clin Nutr 2004;79:362–371.

A review of skeletal and nonskeletal effects of vitamin D deficiency, including CV disease, cancers, type 1 DM, and osteoporosis

166. (4) **Holick MF, Chen TC.** Vitamin D deficiency: a worldwide problem with health consequences. Am J Clin Nutr 2008;87:1080S–1086S.

A review on vitamin D deficiency, including causes, effects, optimal levels, and treatment

167. (1) **Bischoff-Ferrari HA, Dawson-Hughes B, Staehelin HB,** et al. Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials. BMJ 2009;339:b3692.

This meta-analysis of eight randomized controlled trials examining the effect of vitamin D replacement on fall risk in elderly individuals shows that 700 to 1,000 IU of vitamin D daily reduces fall risk in elderly individuals by 19%.

168. (1) **Bischoff-Ferrari HA, Willett WC, Wong JB, Giovannucci E, Dietrich T, Dawson-Hughes B.** Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. JAMA 2005;293:2257–2264.

In this meta-analysis of randomized controlled trials, a vitamin D dose of 700 to 800 IU daily reduced the relative risk of hip fracture by 26% and the relative risk of nonvertebral fractures by 23% compared to calcium or placebo. A vitamin D dose of 400 IU daily did not result in significant fracture reduction.

169. (1) **Avenell A, Gillespie WJ, Gillespie LD, O'Connell DL.** Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. Cochrane Database Syst Rev 2005:CD000227.

This is a cochrane review on the effect of vitamin D supplements in reducing fractures. There was a small reduction in the risk of hip and nonvertebral fractures but not vertebral fractures, when both vitamin D and calcium supplements are given to older people living in institutional care.

170. (4) **Nagpal S, Na S, Rathnachalam R.** Noncalcemic actions of vitamin D receptor ligands. Endocr Rev 2005;26:662–687.

A review of the molecular aspects of the nonskeletal effects of vitamin D and the cell populations where vitamin D receptor was detected

171. (2) **Wang TJ, Pencina MJ, Booth SL,** et al. Vitamin D deficiency and risk of cardiovascular disease. Circulation 2008;117:503–511.

In this prospective cohort of Framingham Offspring study participants, there was a 1.62 hazard ratio of developing CV disease in individuals whose 25-hydroxyvitamin D levels were less than 15 ng/ml compared to those who had a level of 15 ng/ml or higher. The risk was even higher in patients with 25-hydroxyvitamin D less then 10 ng/ml.

172. (2) **Dobnig H, Pilz S, Scharnagl H,** et al. Independent association of low serum 25-hydroxyvitamin D and 1,25-dihydroxyvitamin d levels with all-cause and cardiovascular mortality. Arch Intern Med 2008;168:1340–1349.

In this prospective cohort study of 3,258 patients, low 25-hydroxyvitamin D levels were independent predictors of all-cause and CV mortality. Hazard ratios for all-cause and CV deaths increased with decreasing 25-hydroxyvitamin D levels grouped into quartiles, and the patients with the lowest vtamin D levels had the highest risk.

173. (3) **Reis JP, von Muhlen D, Miller ER III, Michos ED, Appel LJ.** Vitamin D status and cardiometabolic risk factors in the United States adolescent population. Pediatrics 2009;124:e371–e379.

Among 3,577 US adolescents, low vitamin D was associated with a higher risk of hypertension, fasting hyperglycemia, and metabolic syndrome.

174. (2) **Llewellyn DJ, Lang IA, Langa KM,** et al. Vitamin D and risk of cognitive decline in elderly persons. Arch Intern Med 2010;170:1135–1141.

In 858 elderly people, vitamin D deficiency was associated with a higher risk of cognitive decline (HR 1.60 [95% CI, 1.19–2.00]) compared to vitamin D sufficient state.

175. (4) **Holick MF.** Vitamin D status: measurement, interpretation, and clinical application. Ann Epidemiol 2009;19:73–78.

A review of vitamin D metabolism, assessment of nutritional status, and optimal levels for various health benefits

176. (4) **Bischoff-Ferrari HA, Giovannucci E, Willett WC, Dietrich T, Dawson-Hughes B.** Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. Am J Clin Nutr 2006;84:18–28.

A review of optimal vitamin D levels for various health benefits. Based on this review, 25-hydroxyvitamin D levels of at least 30 ng/ml and preferably between 36 and 40 ng/ml are optimal with regard to improving several health outcomes.

177. (4) **Wagner CL, Greer FR.** Prevention of rickets and vitamin D deficiency in infants, children, and adolescents. Pediatrics 2008;122:1142–1152.

A guideline for vitamin D requirements in infants, children, and adolescents

178. (4) **Ross AC, Manson JE, Abrams SA,** et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. J Clin Endocrinol Metab 2011;96:53–58.

Summary of the 2011 IOM report on vitamin D deficiency

179. (4) **Souberbielle JC, Maury E, Friedlander G, Cormier C.** Vitamin D and primary hyperparathyroidism (PHPT). J Steroid Biochem Mol Biol 2010;121:199–203.

A review of the evidence on vitamin D replacement in patients with PHPT

180. (4) **Varghese J, Rich T, Jimenez C.** Benign familial hypocalciuric hypercalcemia. Endocr Pract 2011;17 Suppl 1:13-17.

A comprehensive review of the pathophysiology, clinical manifestations, and approach to diagnosis and management of benign familial hypocalciuric hypercalcemia.

5

Reproductive Disorders

Neil Goodman and Rhoda H. Cobin

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AMENORRHEA

Definition

Amenorrhea is the absence of menstruation in a woman during her reproductive years. Primary amenorrhea is defined as never having menstruated by age 14 without developed breasts and by age 16 with breast development. Secondary amenorrhea is the absence of menses in a woman who has previously had established menstrual function. The length of time defining secondary amenorrhea is widely variable; authorities place it between 3 and 12 months.

Etiology

There is considerable overlap in the causes of primary and secondary amenorrhea since some disorders may begin either before or after puberty and the onset of menses. Ovarian dysgenesis and müllerian defects, including uterine and outlet disorders, account for about 60% of patients with primary amenorrhea. Hyperandrogenic disorders, primary ovarian insufficiency, and hypothalamic amenorrhea account for most patients with secondary amenorrhea. Pregnancy should always be considered as a diagnosis. Constitutional delay of puberty is often responsible for what would otherwise appear to be primary amenorrhea.

Epidemiology

The incidence of primary amenorrhea varies from 0.48% to 1.2%. That of secondary amenorrhea is about 4.9%.

Pathophysiology

The approach to amenorrhea depends on whether it is primary or secondary. In the former, defects may be present at any level of the reproductive system (i.e., hypothalamus, pituitary, ovaries, uterus, or vaginal outflow tract). In women who have had prior menses, it is clear that not only must the woman have had an anatomically normal uterus and outflow tract but that prior normal stimulation with estrogen has occurred, implying ovarian function.

Pregnancy should always be excluded in any patient first seen with amenorrhea, particularly secondary amenorrhea or primary amenorrhea with normal development. Thyroid abnormalities are commonly associated with menstrual disorders and should be sought with an initial thyroid-stimulating hormone (TSH) level.

A history and physical examination will help to define the problem and suggest appropriate laboratory investigation.

Primary Amenorrhea

Vaginal, Uterine, and Ovarian Disorders

Imperforate hymen will be seen with normal growth and development, normal secondary sexual characteristics, and, often, premenstrual molimina and lower abdominal cramping at the time of expected menses. The diagnosis is made by physical examination, and the treatment is surgical hymenectomy.

Müllerian agenesis (Mayer-Rokitansky syndrome) occurs with normal growth and development of secondary sexual characteristics. A rudimentary vaginal canal may be present but with absent uterus and fallopian tubes. Associated abnormalities (including scoliosis, unilateral renal agenesis, and, rarely, cardiac defects) may be found [1]. Although the disorder is usually sporadic, various genetic etiologies have been proposed [2,3]. The diagnosis is made with sonography. Levels of estrogen and gonadotropins are normal. Treatment may include vaginal reconstructive procedures.

Failure of normal ovarian development may be due to Turner syndrome (TS), which may be clinically suspected by the observation of undeveloped secondary sexual characteristics, short stature, and somatic abnormalities including widely spaced nipples, low-set hairline, and other skeletal abnormalities. The diagnosis of an ovarian etiology is confirmed with the finding of an elevated follicle-stimulating hormone (FSH) due to lack of ovarian inhibin production. XO is the most frequent genetic abnormality, but other X chromosome abnormalities and mosaicism may be present. Variants with Y chromosomal material may have mild virilization. The presence of Y chromosome increases the risk of gonadoblastomas, and thus, gonadectomy should be considered [4].

Primary ovarian dysgenesis with XX karyotype is a rare condition that may be inherited as an autosomal recessive trait and does not have the associated somatic features of TS; it may be associated with tall stature. Failure of development of secondary sexual characteristics, ovarian dysgenesis, and normal uterine and vaginal structures are noted. FSH is elevated [5,6].

Rarely, autoimmune oophoritis will be seen as primary amenorrhea, although it is more likely to occur as secondary amenorrhea with evidence of ovarian failure (i.e., elevated FSH). Antiovarian antibodies are sometimes detectable, and a strong association exists with other autoimmune diseases.

Androgen insensitivity syndrome results from mutations in the androgen receptor of varying types and severity with corresponding variation in clinical presentation, including phenotypic females with normal breast tissue, modest axillary and pubic hair, and absent müllerian structures. The incidence is higher in females with inguinal hernias [7,8]. The diagnosis is made with sonography and the finding of a male-range testosterone. The karyotype is XY.

Pituitary/Hypothalamic Disease

Hypogonadotropic hypogonadism (low luteinizing hormone [LH] and FSH) may be seen as primary amenorrhea with or without anosmia (Kallmann syndrome). Various mutations in the KAL gene, which cause abnormal migration of gonadotropin-releasing hormone (GnRH)-producing cells to the hypothalamus have

been described [9]. Other less common syndromes first seen as primary hypogonadotropic hypogonadism include Prader-Willi syndrome and Laurence-Moon-Biedel syndrome.

Pituitary and hypothalamic tumors, especially craniopharyngioma, as well as infiltrative diseases, may rarely begin in childhood presenting as primary amenorrhea, although they usually begin later in life and therefore after menses have begun (vide infra).

Secondary Amenorrhea

Vaginal/Uterine Disorders

In patients with previously normal menses, secondary amenorrhea with normal hormonal function and abnormal uterine function may develop. A history of pelvic infection, dilation and curettage, or uterine instrumentation in a patient with secondary amenorrhea should suggest Asherman syndrome. The absence of bleeding after estrogen/progesterone therapy implies that a functional endometrium is absent. Hysteroscopy or hysterosalpingography may be required to establish the diagnosis.

Ovarian Failure

Autoimmune oophoritis will occur as secondary amenorrhea with evidence of ovarian failure (i.e., elevated FSH). Antiovarian antibodies are sometimes detectable, and a strong association with other autoimmune diseases is present [10,11]. Premature ovarian failure is a feature of the fragile X syndrome. Genetic analysis and counseling are required. Premature ovarian failure may be familial and may be found with no evidence of autoimmune disease.

Pituitary and Hypothalamic Disease

Women with normal or low gonadotropins, normal pelvic structures, and normal androgens may be suspected of having hypothalamic or pituitary disease. Although the latter is often functional, it is imperative to image the pituitary with CT or MRI to rule out pituitary tumors or other lesions in this area, which may affect normal hypothalamic–pituitary function. Usually, this is seen as secondary amenorrhea, although occasionally, the onset is early enough in life to appear as primary amenorrhea.

A high prolactin level may indicate either prolactin production from a pituitary adenoma or stalk compression, causing reduced dopaminergic negative regulation of pituitary prolactin production. Because the level of prolactin is usually proportionate to the size of the tumor in pure prolactin-secreting tumors, tumors disproportionately large compared with the serum prolactin level should be suspected of being nonprolactinomas, which are not amenable to therapy with dopaminergic agents and may be considered for surgery.

Hypothalamic amenorrhea is a very common cause of secondary amenorrhea and an occasional cause of primary amenorrhea. Laboratory studies reveal normal to low gonadotropins and estrogen and normal androgens and prolactin levels. Anatomic pathology is absent. A thorough and sensitive history must be obtained because emotional stress, excessive exercising, weight loss, dieting, and eating disorders such as anorexia and bulimia may be difficult to elicit on initial history. Once rapport is established, the patient may be more comfortable in discussing these important etiologic factors and their management.

Hyperandrogenism

Excessive androgen production is associated with both primary and secondary amenorrhea and may be due to either ovarian or adrenal sources.

The most common cause of primary amenorrhea with excess androgen production is adrenal hyperplasia, most frequently 21-hydroxylase deficiency. The

frequency of this disorder is variable, depending on ethnic origin. Presentation may be at birth with ambiguous genitalia, or it may be delayed until later in life, particularly in the non–salt-wasting variety. In childhood, accelerated growth and bone maturation and signs of hyperandrogenism (hirsutism, acne, increased musculature, alopecia) appear. If untreated, amenorrhea and short final adult stature are found (because of early closure of the epiphyses secondary to androgenic stimulation). The diagnosis is made with the finding of elevated 17-OH progesterone, either in the basal state or with adrenocorticotropic hormone (ACTH) stimulation. Genetic testing will confirm the presence of a variety of mutations of the CYP21 gene on chromosome 6 [12]. Treatment consists of glucocorticoid replacement to suppress excess ACTH and hence adrenal androgen production, with care to avoid excess glucocorticoid, which can cause growth retardation, osteopenia, and iatrogenic Cushing disease [13,14].

Other less common enzyme defects causing adrenal hyperplasia include: 11-hydroxylase deficiency, which occurs with amenorrhea, hyperandrogenism, hypertension, and hypokalemia; 3β-hydroxysteroid dehydrogenase deficiency, which causes hyperandrogenism; and 17-hydroxylase deficiency, which occurs with sexual infantilism.

Polycystic ovarian syndrome (PCOS) affects between 6% and 10% of women of reproductive age and typically occurs with oligomenorrhea dating from the onset of puberty, along with variable hyperandrogenism. PCOS is strongly associated with insulin resistance and carries a high risk of glucose intolerance, frank diabetes, hypertension, dyslipidemia, and an increased frequency of myocardial infarction and cerebrovascular disease in later life; making a diagnosis is critical [15].

Signs or symptoms of hyperandrogenism may include acne, hirsutism, and alopecia. More severe hyperandrogenism (virilization) including increased muscle mass, clitoromegaly, deepening of the voice, and male-pattern baldness is indicative of higher testosterone levels (vide infra), usually not seen with PCOS.

Diagnosis

Androgen concentrations including total and free testosterone, androstenedione, and dehydroepiandrosterone sulfate (DHEA-S) should be measured. A testosterone level between 40 and 200 mg/ml is consistent with diagnosis of PCOS or other forms of hyperandrogenemia. A testosterone level more than 200 mg/ml suggests an ovarian tumor, adrenal tumor, or hyperthecosis; therefore, appropriate imaging studies are needed. An elevated DHEA-S level may indicate adrenal hyperandrogenism or an adrenal tumor.

17α-Hydroxyprogesterone elevation either in the basal state or after ACTH stimulation will make a diagnosis of 21-hydroxylase adrenal hyperplasia, the most common variety of acquired adrenal hyperplasia.

Treatment

Therapy for amenorrhea should be directed at the underlying cause. If outflow obstruction or Asherman syndrome is present, surgical consultation with a gynecologist is needed. For ovarian failure secondary to gonadal dysgenesis with a Y chromosome or fragment, surgical removal of the gonads at the time of diagnosis has been recommended because of the high risk of gonad-related malignancy. In androgen insensitivity syndrome, removal of the gonads may be deferred until immediately after pubertal maturation because the risk of malignancy appears to be low until after puberty [16]. Psychological counseling is also needed in patients with gonadal dysgenesis and androgen insensitivity syndromes.

Management of TS is complex and focuses on recognizing and monitoring the associated anomalies [17]. About 30% of patients with TS have congenital heart

defects (e.g., bicuspid aortic valve and coarctation of the aorta), and 30% have renal anomalies. The risk of death from aortic aneurysm is high (relative risk [RR] of 63.23, with a 95% confidence interval [CI] of 20.48–147.31), and an initial evaluation with periodic echocardiography and follow-up by a cardiologist are needed [18]. Thyroid disease, usually Hashimoto disease, may occur in up to 30% of affected patients; therefore, TSH levels should be measured every 1 to 2 years or if symptoms suggestive of thyroid disease develop. Short stature can be improved significantly with the early use of growth hormone, and consideration for use should be given if and when the height is less than the 5th percentile or as indicated based on specific clinical features [13,19]. Estrogen use will cause fusion of the epiphyses and may therefore limit final adult height (AH), depending on the total length of growth hormone therapy before starting estrogen [20]. However, starting growth hormone early may allow the use of estrogen at age 12 or 13 without compromising height gain [21]. Early use of estrogen may have some benefit on motor and nonverbal function in girls with TS [22], although this must be reconciled with the goal of increasing height. Bone-density studies should be done in adults and periodically thereafter [17]. Patients with TS, particularly primarily those with mosaicism, may rarely conceive spontaneously, though the outcomes of pregnancy often include chromosomal abnormalities, congenital anomalies, and fetal loss [23,24]. The potential for pregnancy does not improve with medical interventions [25]. Ovum donation has allowed successful pregnancy outcomes in many women with Turner syndrome, but it is critical to detect somatic abnormalities, particularly cardiac disease, before embarking on a course of assisted fertility. Cyclic hormone replacement therapy (HRT) is justified by recent studies that suggest a beneficial effect of estrogen therapy on bone density and fracture risk in such patients [26–31].

Nonsecretory pituitary tumors and tumors producing growth hormone or ACTH (Cushing syndrome) tumors may require surgical therapy, whereas the majority of prolactin-secreting tumors may be managed medically with dopamine agonist therapy. Treatment of adrenal hyperplasia consists of replacement glucocorticoid to suppress ACTH and hence adrenal androgen production while avoiding excessive steroid levels, which may cause growth retardation. In extremely rare situations with poor response to medical therapy, adrenalectomy may be required. A recent evidence-based guideline has been published and should be consulted for detailed therapy [32]. Ovarian and adrenal tumors are treated surgically. PCOS therapy is discussed in the section on hirsutism.

Hypothalamic dysfunction should be treated by addressing the underlying cause wherever possible. Weight gain in patients with anorexia may help normalize reproductive function and bone density [33,34]. HRT is often initiated to optimize bone development in the setting of hypothalamic dysfunction, but results have been inconsistent [35]. More recent studies find that hormone replacement alone does not improve bone density, whereas weight gain and/or the administration of recombinant IGF-1 may lead to improvement both in markers of bone formation and in bone density [35,36]. Baseline leptin, IGF-1, and androgen levels are predictive of bone microarchitecture, independent of body mass index (BMI) [37]. Nutritional counseling as well as psychological counseling may be necessary, and modification of exercise regimens may be helpful.

Table 5.1 is a summary of amenorrhea.

HYPERANDROGENISM AND PCOS

Hyperandrogenism

Hyperandrogenism describes the reaction of the pilosebaceous units of the skin when stimulated by androgens. The skin reacts by excessive hair growth in a

Table 5.1. Amenorrhea Summary

	Uterus	FSH	Prolactin	Testosterone	Karyotype	Treatment
Primary Amenorrhea						
Turner syndrome	Yes	↑	N	N	45,X; mosaic variants	Counseling; HRT consideration; CV evaluation; thyroid tests; GH? and discussion if appropriate
Immune ovarian failure	Yes	↑	N	N	46,XX	HRT?
Gonadal dysgenesis	Yes	↑	N	N	46,XX; 46,XY	remove gonads if Y or part of Y chromosome present
21α-Hydroxylase deficiency	Yes	N	N	↑	46,XX	Glucocorticoids
17α-Hydroxylase deficiency	Yes	N	N	N	46,XX	Glucocorticoids; HRT
Androgen insensitivity	Yes	N	N	↑	46,XY	Remove gonads
Müllerian agenesis	No	N	N	N	46,XX	Surgical consideration; evaluate for urinary tract anomalies
Kallmann syndrome	Yes	N,↓	N	N	46,XX	hMG/GnRH for fertility
Hypothalamic dysfunction	Yes	N,↓	N	N	46,XX	hMG/GnRH for fertility if primary disease not treatable
Prolactinoma	Yes	N	↑	N	46,XX	Dopamine agonists, surgery
Other pituitary tumor	Yes	N,↓	N,↑	N	46,XX	Surgery, irradiation
Infiltrative disorders	Yes	N,↓	N,↑	N	46,XX	Treat disease
Secondary Amenorrhea						
Premature ovarian failure	Yes	↑	N	N	46,XX	HRT

Continued

Table 5.1. Amenorrhea Summary *(Continued)*

	Uterus	FSH	Prolactin	Testosterone	Karyotype	Treatment
Iatrogenic: radiotherapy, chemotherapy	Yes	↑	N	N	46,XX	HRT
Low body weight/exercise	Yes	N,↓	N	N	46,XX	Weight gain as appropriate
Hypothalamic dysfunction	Yes	N,↓	N,↑	N	46,XX	HRT, hMG/GnRH if cannot treat underlying disease for fertility
Sheehan syndrome	Yes	N	N	N	46,XX	HRT, hMG/GnRH if cannot treat underlying disease for fertility
Prolactinoma	Yes	N	↑	N	46,XX	Dopamine agonists, surgery; hMG if hypopituitary for fertility
Hyperprolactinemia	Yes	N,↓	↑	N	46,XX	Change of medications possible? Treat underlying medical problem
Other pituitary tumor	Yes	N,↓	N,↑	N	46,XX	Surgery, irradiation
Infiltrative disorders	Yes	N	N,↑	N	46,XX	Treat disease
PCOS	Yes	N	N,↑	N,↑	46,XX	See section on weight control; metformin; OCT
Asherman syndrome	Yes	N	N	N	46,XX	Surgery if appropriate

GH, growth hormone; GnRH, gonadotropin-releasing hormone; hMG, human menopausal gonadotropin; HRT, hormone replacement therapy; N, normal; PCOS, polycystic ovarian syndrome.

male pattern distribution (hirsutism), acne, or hair loss (alopecia). However, the finding of hyperandrogenism does not define excess androgen production but can be a significant indicator of the presence of an androgen excess disorder, leading to the measurement of testosterone and other androgens, evaluating if there is an overproduction by the ovaries or adrenal glands. Hirsutism may occur without actual elevation in androgen levels if increased target organ sensitivity to androgen action exists. It should be noted that ethnic differences in the number of hair follicles present and individual skin sensitivity of the pilosebaceous unit to androgens are major determinants of the presence of hirsutism, as well as acne and androgenic alopecia [38].

Hirsutism should not be confused with hypertrichosis, which is defined as the growth of hair on any part of the body, in excess of the amount usually present in persons of the same age, race, and sex. Extreme excess of androgen production will present as virilization, in which hirsutism is accompanied by male-pattern baldness, deepening of the voice, increased muscle development, and clitoromegaly. The presence of true virilization usually points to a serious underlying disorder, such as virilizing tumors of the ovary or adrenal gland or hyperthecosis ovarii [39].

Girls with severe acne that is persistent or exacerbates in the mid-20s or 30s or that is resistant to oral and topical agents have a high incidence of hyperandrogenemia and a 40% likelihood of having PCOS [40,41]. Androgenic alopecia typically presents as thinning of the anterior midline area of the scalp and extends posteriorly to the midvertex of the scalp. The frontal hair line is usually preserved, and a triangular pattern of hair thinning (triangle sign) is often noted in the anterior midline area. Alopecia is present in 40% to 70% of women with PCOS [42].

PCOS

The most common form of hyperandrogenism is the polycystic ovary syndrome (PCOS). This heterogeneous syndrome is the most frequently encountered endocrine disturbance in women of reproductive age. The prevalence of PCOS ranges from 5% to 10% [43], and it affects all ethnic groups. PCOS is not only a reproductive disorder but also a metabolic one [44].

Defining the syndrome includes four issues: oligomenorrhea, clinical and biochemical features of hyperandrogenism, polycystic ovaries by ultrasonography, and the exclusion of other causes associated with androgen excess (nonclassical congenital adrenal hyperplasia (NCCAH), virilizing syndromes of the ovary or adrenal, and Cushing syndrome). The consensus is that oligomenorrhea and hyperandrogenism are essential components of the syndrome [45]. The specificity of morphologic evidence of polycystic ovaries on ultrasonography is limited since 23% of apparently normal women have characteristic findings of polycystic ovaries [46].

Disruption of the female reproductive system in PCOS typically begins at menarche, with menstrual cycles longer than 35 to 40 days or fewer than 10 periods per year, defined as oligomenorrhea. The irregular menses may be interspersed with episodes of what appear to be regular cycles (not necessarily ovulatory) and may also be associated with episodes of heavy dysfunctional intermenstrual bleeding [45].

PCOS AND INSULIN RESISTANCE (METABOLIC SYNDROME)

The pathophysiology of the menstrual irregularities and hyperandrogenism of PCOS includes hypothalamic–pituitary abnormalities that result in GnRH and LH dysfunction and a primary enzymatic defect in ovarian or combined ovarian and adrenal steroidogenesis. Observational studies of obese women with PCOS have found an increased risk for developing impaired glucose tolerance (IGT)

(31%–35%) and type 2 diabetes mellitus (DM) (7.5%–10%) [47]. With 50% to 70% of all women with PCOS having some degree of insulin resistance [48], a hypothesis to explain these aspects of PCOS therefore follows that this metabolic disorder of compensatory hyperinsulinemia exerts adverse effects on the hypothalamus, pituitary, ovaries, and, possibly, adrenal glands, explaining the oligomenorrhea and hyperandrogenemia.

There are serious health consequences beyond dermatologic and reproductive dysfunction secondary to the insulin resistance, which are defined by the metabolic syndrome [49]. The metabolic syndrome includes:

- Glucose intolerance/diabetes
- Elevated blood pressure level (≥130/85)
- Increased waist circumference (≥35 inches or waist-to-hip)
- Reduced high-density lipoprotein cholesterol level (≤50 mg/dl)
- Elevated triglyceride levels (≥150 mg/dl)

All women with PCOS should be screened with a 2-hour (75-g) glucose tolerance test [50], with rescreening every 1 to 2 years because of the high rates of conversion to IGT and diabetes. Of clinical note is that acanthosis nigricans with or without skin tags are markers of hyperinsulinism and the MS [51].

Diagnosis

Laboratory testing in PCOS can establish hyperandrogenemia and exclude other disorders than can have similar clinical characteristics. Tests include determinations of plasma total and free testosterone levels, serum levels of luteinizing and FSHs, and measurement of sex hormone-binding globulin (SHBG), DHEA-S, and 17-hydroxyprogesterone. Additional laboratory tests may include plasma prolactin, insulin, thyroid function studies, and cortisol levels.

There is no standardized testosterone assay in the United States in the female range [52], causing lack of sensitivity and reliability in measuring testosterone. Subsequently, there is no universal normative standard for testosterone values that defines hyperandrogenemia. In a highly sensitive assay, using tandem mass spectrometry, most patients with clinical hyperandrogenism will have testosterone levels greater than 40 ng/dl [53,54]. Reference ranges reported by commercial laboratories can include an upper limit of normal of 90 ng/dl, and therefore, many women with hyperandrogenemia would be classified as having a normal testosterone. For the clinician trying to resolve this testosterone measurement problem, look for a commercial lab that utilizes tandem mass spectrometry. At this time, the Center for Disease Control is working with commercial labs to establish a universal standard for measuring testosterone.

Treatment

Goals of therapy include:

- Manage hyperandrogenism through reduced androgen production and blockage of androgen action
- Improve reproductive function
  - Control of menstrual disorders
  - Ovulation induction
- Ameliorate complications putatively due to insulin resistance
  - Glucose intolerance
  - Dyslipidemia
  - Hypertension
  - Atherogenesis
- Weight management

Lifestyle changes are recommended to encourage weight loss if the patient is overweight. Appropriate diet and exercise programs should be instituted in such patients and can be effective in controlling these disorders, including the associated hirsutism [55]. In obese PCOS patients, wieght loss with or without exercise may improve clinical manifestations; as little as 5-10% weight loss may often result in significant improvement. Weight loss is the best intervention for diabetes prevention and should be the first line of therapy for all obese PCOS. In women with PCOS and morbid obesity, gastric bypass should be considered.

Nonpharmacologic therapy for hirsutism includes hair removal by shaving, depilatories, bleaching, waxing, and photothermolysis. Topical ornithine decarboxylase inhibitors that theoretically slow hair growth by inhibiting an essential step in hair formation within the hair follicle may also be effective [56], but the terminal hairs typically reappear within a few weeks after cessation of the drug.

Hormonal contraception, combined estrogen and progestin formulations, is the most effective therapy for hyperandrogenism and menstrual irregularities. The mechanisms of action of oral contraceptives include: (1) suppression of ovarian androgen production: (2) increasing SHBG (sex hormone binding globulin) which reduces bioavailable free testosterone; and (3) the direct anti-androgenic activity of some progestins such as cyproterone and drosperinone [57]. The combination pill ethinyl estradiol/drospirenone is Food and Drug Administration (FDA)-approved for the treatment of moderate to severe acne. The effective contraception from hormonal contraception allows for the addition of other antiandrogen medications that are contraindicated in pregnancy. Since antiandrogenic compoounds including spironolactone, cyproterone and others are dangerous to a developing make fetus, they are contraindicated during pregnancy. Therefore, effective contraception using OCPs may allow the safe introduction of additional anti-androgens if clinically necessary.

Antiandrogens antagonize the binding of testosterone and other androgens to the androgen receptor. Spironolactone is an antiandrogen that inhibits testosterone binding at the receptor level. It is rated as pregnancy category C by the U.S. FDA. In a review of six small, randomized, controlled trials, a significant benefit was noted after 6 months of taking spironolactone, 100 mg/d, compared with placebo [59]. The effects of spironolactone on hirsutism are at least comparable with those of flutamide and finasteride [60]. Spironolactone is often combined with an oral contraceptive pills (OCP) to help prevent pregnancy, to maintain regular menstrual cycles, and to augment therapeutic efficacy. Cyproterone acetate is a progestin that acts as an antiandrogen and is frequently used worldwide for hirsutism, but it is not available in the United States. Other antiandrogens and some OCPs have been demonstrated to be as effective as cyproterone acetate in most studies [61]. Flutamide is an antiandrogen that inhibits testosterone binding at the receptor level. It is FDA category D for pregnancy. It is as effective as spironolactone and finasteride in treatment of hirsutism [62]. Use of this agent in hirsutism should be limited to investigational studies because of the lack of improved efficacy, the potential for hepatic toxicity, the high cost, and its potential for fetal harm.

Finasteride inhibits 5α-reductase, which controls the conversion of testosterone to dihydrotestosterone. Although it is specific for the enzyme type found in the prostate, it has clinical effects on decreasing hair growth as well. It is FDA category X for pregnancy, showing fetal risk, and is therefore contraindicated in pregnancy and in women at risk for pregnancy. For hirsutism, it is slightly less effective in most studies compared with spironolactone and flutamide, although it may provide additional improvement in combination with some antiandrogenic OCPs [59,62]. Side effects are minimal and the associated use of an oral contraceptive is mandatory. The effective dosage in women is 2.5 to 5 mg taken once daily.

Finasteride has some efficacy in the treatment of androgenic alopecia [63].

Insulin-Sensitizing Drugs

As discussed above, the pathophysiology of menstrual dysfunction and hyperandrogenism/hyperandrogenemia of PCOS is directly related to the hyperinsulinism of insulin resistance. Therefore, by treating PCOS with an insulin-sensitizing drug, a decline in insulin levels should restore reproductive function and reverse the hyperandrogenemia. Metformin (MET) is an oral biguanide approved for the treatment of type 2 diabetes. MET treatment [64,65] in PCOS has been shown to improve menstrual cyclicity, reduce testosterone and free testosterone levels, and enhance fertility potential, especially when combined with clomiphene.

Trials of the effectiveness of MET for weight loss in PCOS have had mixed results with either no difference from placebo or modest reductions [66,67].

Thiazolidinediones (TZDs), rosiglitazone and pioglitazone, have insulin-sensitizing activity, reducing plasma insulin and androgen levels, and frequently improve hirsutism and menstrual abnormalities, although these drugs are not FDA approved for use in PCOS patients in the absence of diabetes mellitus [68–70]. Recent safety concerns with TZDs have limited the "off-label" use of these agents in PCOS.

PRECOCIOUS PUBERTY

Definition

Precocious puberty is defined as the premature development of secondary sex characteristics. In girls, this generally constitutes breast budding (thelarche) or development of pubic hair (pubarche) before age 7 in whites and age 6 in blacks. In boys, testicular enlargement before age 9 would indicate precocious puberty [71].

In contrast, premature adrenarche refers to inappropriately early development of axillary and pubic hair, whereas premature thelarche refers to early breast development. Either or both may be associated with true precocious puberty, which is associated with progressive development, accelerated growth velocity, and ultimately menses in girls. Whereas precocious puberty leads to premature closure of the epiphyses and short adult final stature, the former two conditions are not progressive and do not carry this risk. They are generally static, and children enter full puberty at a normal age.

Pathophysiology

Central precocious puberty (CPP) is defined as early activation of pulsatile GnRH activity in an otherwise normal hypothalamopituitary–gonadal axis. Pseudopuberty occurs when true central activation is absent.

Etiology and Diagnosis

Premature adrenarche and thelarche are characterized by prepubertal LH, FSH, testosterone, and estradiol levels, without progression of bone age. In premature adrenarche, a significantly elevated DHEA-S level requires further evaluation for CAH or adrenal tumor. Girls with premature adrenarche may be at risk for PCOS and insulin resistance. Periodic monitoring for both conditions is indicated to ensure they do not progress.

In girls, CPP is overwhelmingly idiopathic but may result from a hypothalamic hamartoma with pulsatile GnRH secretion. Bone-age testing should be undertaken to assess the effect on growth rate and to gauge progression and response to therapy. MRI of the brain/pituitary is needed in all cases of CPP to exclude disease affecting the central nervous system. In boys, CPP is nearly always secondary to a tumor, irradiation, or septooptic dysplasia with premature activation

of GnRH secretion. Discontinuation after exposure to exogenous sex steroids may also result in activation of the central axis, resulting in acquired CPP. MRI of the brain and hypothalamopituitary region should be done, as well as a bone-age test.

Pseudopuberty in girls is associated with prepubertal levels of LH and FSH, LH unresponsive to GnRH stimulation, and sex hormones in the pubertal range or higher. Causes in girls include ovarian follicular cysts, McCune-Albright syndrome (associated with café-au-lait spots and polyostotic fibrous dysplasia), and stromal cell tumors of the ovary. A pelvic ultrasound should be done to look for cysts or masses in the ovary. Thyroid studies should be done to evaluate for hypothyroidism.

In boys, autonomous testicular function may be present secondary to a Leydig cell tumor, human chorionic gonadotropin (hCG)-secreting tumor, McCune-Albright syndrome (activated G protein), or familial male precocious puberty caused by an activating mutation of the LH receptor expressed in testicular Leydig cells. LH and FSH levels will be in the prepubertal range, with pubertal range or higher testosterone levels. With a Leydig cell tumor, a testicular mass may be noted on examination or ultrasound. An hCG level should be checked in boys with precocious puberty because tumors that secrete hCG can stimulate testicular testosterone production. These tumors may occur in the gonads, pineal, liver, posterior mediastinum, or retroperitoneum.

Other causes of pseudopuberty include abuse of exogenous androgens, congenital adrenal hyperplasia (CAH), and a pituitary gonadotroph-secreting adenoma. Thyroid studies (TSH, FT4) should be done to evaluate for hypothyroidism.

Treatment

For all patients with precocious puberty, it is important to provide the child and family with professional counseling services, although no formal studies have been reported with clinical outcomes. Patients with isolated premature thelarche or premature adrenarche should be examined periodically to ensure that precocious puberty is not developing. Girls with premature adrenarche should be monitored especially for development of the PCOS and the insulin-resistance syndrome. Treatment of pseudoprecocious puberty must be directed at the underlying disease. Surgery, irradiation, and chemotherapy options exist for tumors causing precocious puberty. Aromatase inhibitors may be used for gonadotropin-independent precocious puberty [72,73].

Treatment of boys with familial male-limited precocious puberty with spironolactone and testolactone helps controls symptoms of acne, erectile function, and aggression but without a significant improvement of predicted final adult height (AH) [74]. Activation of the central axis with development of CPP in response to circulating sex hormones limits the usefulness of this combination alone. Combination of spironolactone and testolactone with a GnRH agonist to prevent the activation of the central axis is more effective, with an improvement in final predicated AH [75]. The use of combination therapy with bicalutamide, an antiandrogen, and a third-generation aromatase inhibitor (anastrozole or letrozole) has been shown to reduce virilization, reduce bone age acceleration, and allow continued linear growth [76,77].

In a small study, resistant cases may respond to ketoconazole [78].

No unanimity exists about treatment of CPP. Treatment goals include the preservation of the potential for normal AH, prevention of premature sexual activity, improvement of psychosocial problems related to the disorder, and prevention of early menarche [79]. Proposed criteria for therapy with GnRH agonists are as follows: patients that clearly meet the definition for precocious puberty with documentation of an active GnRH axis by GnRH stimulation testing or sleep studies

and sex hormone levels in the pubertal range with limited predicted adult height (PAH) (<5th percentile) or significant psychosocial problems from menses or early development [80]. Generally, therapy is initiated in very young children to prevent sexual development and in older children when bone-maturation acceleration outpaces linear growth velocity, resulting in premature closure of the epiphyses and diminished final AH. No studies document the benefits of gonadotropin releasing hormone (GnRH) therapy on ultimate psychosocial well-being in children with this disorder. Quality-of-life issues should enter into therapy considerations but must be individualized and have not been well studied. Long-term safety issues pertaining to the use of GnRH agonists are largely unknown. A review of earlier trials of GnRHa use suggests that therapy should be started before age 8 years to have a significant impact [79]. Therapy with GnRHa generally produces a height increase of 3 to 8 cm over that in untreated patients but typically 1 to 7 cm below the normal PAH. Newer studies suggest that a final AH appropriate for midparental height prediction is achieved by 85% to 90% of patients. Although some studies suggest that weight gain may be associated with therapy with GnRH analogues [81,82], two recent large trials of GnRH therapy in 121 girls over 1 year revealed that GnRH therapy did not reverse the accretion of bone mass nor did obesity occur. Body composition and later menstrual function were normal and progression to PCOS was not observed [83,84].

Addition of growth hormone in small studies has generally shown significantly improved heights in girls [85–87] but has not been clearly shown to have value in boys, although sample sizes in the studies have been small. Larger, more recent studies suggest a therapeutic benefit with a gain between pretreatment predicted adult height (PAH) and final height (FH) of 8.2 ± 4.8 cm according to tables for accelerated girls and 12.7 ± 4.8 cm according to tables for average girls in patients treated with GH plus GnRHa. In patients treated with GnRH alone, the gain calculated between pretreatment PAH for accelerated girls was just 2.3 ± 2.9 cm and 7.1 ± 2.7 cm greater than pretreatment PAH for average girls. The difference between the gain obtained in the two groups (~6 cm) remained the same however the PAH was calculated [88]. The most powerful predictors of a good response are early age of disease, early age at therapy, rapidity of bone advancement, and initial predicted height to target height deficit [89]. The use of different assessment tools for evaluation of current bone age may be important in determining those children who would most benefit from the combination of GnRH analogues and growth hormone [90].

MALE HYPOGONADISM

Definition

Hypogonadism is inadequate gonadal function, testicular insufficiency, as manifested by deficiencies in sperm production and/or the secretion of sex steroids. Therefore, hypogonadism may manifest with testosterone deficiency, infertility, or both conditions.

Symptoms and signs of testosterone deficiency include:

- Reduced libido and sexual activity
- Lack of effect of PDE5 inhibitors for erectile dysfunction
- Reduced muscle mass and strength
- Depressed mood
- Decreased energy or vitality; increased fatigue
- Osteoporosis/low bone mass

Etiology and Diagnosis

Disorders of male hypogonadism are generally divided into hypogonadotropic hypogonadism and hypergonadotropic hypogonadism. Hypogonadotropic disorders are associated with inappropriately normal or low FSH and LH levels in the face of low androgen levels, while hypergonadotropic refers to elevated gonadotropin levels.

The initial hormonal evaluation of hypogonadism should include FSH, LH, testosterone (preferably morning sample), free testosterone, and prolactin levels (Table 5.2). Measurement of total testosterone includes free and protein bound, with a normal range of 300 to 1,000 ng/dl. Free testosterone, as measured by equilibrium dialysis, is considered low if less than 50 to 70 ng/dl. Bioavailable testosterone (non-SHBG) is the free plus albumin-bound fraction and can be estimated using a measurement of SHBG since accurate free testosterone measurements are difficult to obtain. Concentrations of FT and bioT can also be calculated from the total testosterone and SHBG level by use of one of several published algorithms (http://www.issam.ch). Measurements of free or bioavailable testosterone are particularly useful in the aging male population since total testosterone concentrations tend to decrease and SHBG concentrations increase. Since there can be significant interassay variation in testosterone measurements, there is an ongoing national project to validate all testosterone clinical measurements, as noted in the section on PCOS.

MRI of the brain and pituitary may be needed to evaluate further for secondary causes:

- Severe secondary hypogonadism (TT < 150 ng/dl)
- Hyperprolactinemia (Table 5.3)
- Other pituitary-hormone deficiency (panhypopituitarism)
- Symptoms/signs of tumor-mass effect (headache, visual-field defect, or impairment)

Congenital Male Hypogonadism

Congenital male hypogonadism is seen with failure of sexual development. Hypogonadotropic disorders have absent or abnormal GnRH secretion and may occur in the setting of anosmia (Kallmann syndrome, 1/10,000). Other syndromes include Prader-Willi syndrome and Lawrence-Moon-Biedel syndrome. Gonadotropin levels (LH/FSH) are low in defects in androgen synthesis or action. Congenital causes of hypergonadotropic hypogonadism, primary testicular insufficiency (with high LH and FSH), include Klinefelter syndrome (47,XXY and other variants), other chromosomal abnormalities, cryptorchidism (8/1,000), and sickle cell disease.

Acquired Male Hypogonadism

Acquired hypogonadotropic disorders include prolactinomas and other pituitary tumors, infiltrative disorders such as sarcoidosis, histiocytosis or hemochromatosis, infection, pituitary apoplexy, injury, severe illness, glucocorticoids, pituitary surgery, irradiation, and aging.

Hypergonadotropic disorders are associated with high FSH and LH levels. Acquired testicular insufficiency with compensatory hypergonadotropin secretion may result from muscular dystrophy, mumps orchitis, HIV, testicular trauma, torsion, chemotherapy, chronic diseases, or irradiation. Many cases are idiopathic.

Testosterone deficiency associated with aging (late-onset hypogonadism or andropause) constitutes the largest group of men who present for evaluation of androgen deficiency. Epidemiologic studies have revealed that aging in men

Table 5.2. Male Hypogonadism Disorders: Evaluation and Therapy Considerations

Testicular Size*	FSH	LH	Testosterone†	Semen Analysis	Diagnosis	Evaluation of Treatment
Not palpable	↑	↑	↓	Azoospermia	Anorchism	Surgical exploration
Not palpable	↑	↑	N†/↓	Azoospermia	Bilateral cryptorchidism	Surgical exploration
<5 ml	↓	↓	↓	Azoospermia, oligospermia	Kallmann syndrome, hypogonadotropic hypogonadism	T to virilize; hCG, hMG (or FSH) or GnRH for spermatogenesis
<5 ml	↑	↑	N†/↓	Azoospermia	Klinefelter syndrome; other hypergonadotropic syndromes	Karyotype to confirm; T to virilize
8–15 ml	↑	N	N	Azoospermia, oligospermia	Germinal damage; toxins, idiopathic	Fertility: IVF with ICSI(?)
10–20 ml	↓	↓	↓	Oligospermia	Adult acquired hypogonadotropic hypogonadism	Pituitary MRI; prolactin. Treat pituitary disorder if present; otherwise treat as Kallmann syndrome
10–20 ml	N/↑ (variable)	N†/↑ (variable)	N/↓	Variable	Senescence	T if symptomatic with low TB
15–20 ml	N/↑	N	N	Oligospermia	Varicocele, drugs, idiopathic	Fertility; varicocele repair if significant varicocele present. Optimize wife; IVF with ICSI
Variable phenotype	↑ (variable)	↑ (variable)	↑	Variable	T receptor defects, Reifenstein syndrome	Variable (depending on degree); medical or surgical therapy

* Normal testicular size is 20–30 ml. Testicular size is used here as a clinical finding to help narrow the differential diagnosis. Some variation beyond the listed ranges may exist for a specific condition. Use of this variable is optional; the diagnosis should be based on the total clinical picture.

† Because of changes in SHBG levels, total testosterone may be in the normal range in the setting of low testosterone production. An SHBG level or free testosterone should be used in this setting to determine whether treatment options should be considered.

FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; hCG, human chorionic gonadotropin; hMG, human menopausal gonadotropin; ICSI, intracytoplasmic sperm injection; IUI, intrauterine insemination; IVF, in vitro fertilization; LH, luteinizing hormone; MRI, magnetic resonance imaging; N, normal; SHBG, sex hormone-binding globulin; T, testosterone.

Adapted from American Association of Clinical Endocrinologists. Medecal Guidelines for clinical practice for the evaluation and treatment of hypogonadism in adult male patients—2002 update. Endocr Tract 2002;8:440–456.

Table 5.3. Medications That Can Cause Hyperprolactinemia

Dopamine receptor blockers
Catecholamine or dopamine depletors
Phenothiazines and other neuroleptics
Antidepressants
Antihypertensives
Estrogens
Opiates

is accompanied by a progressive decline in total and free testosterone levels. Approximately 30% of men 60 to 70 years old and 70% of men from 70 to 80 years old have low bioavailable or free testosterone levels [91,92], but the level of testosterone that defines the threshold when symptoms are a result of testosterone deficiency is unclear. Symptoms and signs of testosterone deficiency may be difficult to differentiate from aging and/or depression. Androgen deficiency is associated with many chronic diseases including type 2 diabetes (insulin resistance/metabolic syndrome), visceral adiposity, hypertension, hyperlipidemia, and cardiovascular disease, all of which have been shown to improve with testosterone supplementation. In addition, studies have shown increased mortality rates in men with androgen deficiency [93,94]. As discussed above, the lack of precision and reproducibility of the testosterone assay, along with the absence of accurate normative data, make the diagnosis of late-onset hypogonadism challenging and controversial.

A recent study of late-onset hypogonadism [95] defined a low testosterone level of less than 320 pg/dl based on the presence of at least three symptoms of decreased sexuality. Other studies have found only weak associations with physical symptoms and low testosterone. However, low testosterone levels were inversely associated with coronary artery disease, visceral fat, diabetes, and mortality [93].

Therefore, to make a diagnosis of androgen deficiency, measure testosterone and bioavailable or free testosterone only in men with signs and symptoms of testosterone deficiency. Sexual and physical symptoms are more informative than behavioral and psychological symptoms. Obtain a morning sample for analysis, and seek out a laboratory that can perform assays using tandem mass spectrometry. Repeat the analysis for confirmation.

Studies treating elderly men with low serum testosterone with testosterone have shown that men with clinical symptoms identical to the symptoms of classic hypogonadism will benefit most from such therapy. Therefore, it is the general consensus to treat men with age-related hypogonadism only when clinical symptoms are present that can be potentially corrected by testosterone administration [96].

Treatment

The goals of testosterone therapy are:

- Normalization of testosterone levels
- Improved libido
- Positive effects on fatigue (improved energy level)
- Improved mood, sense of well-being
- Increase in lean body mass and strength
- Decrease in body fat mass
- Improved bone mineral density (BMD) (effects on fracture risk are currently unknown)

Treatment should be directed first at any underlying disorders. The goal of therapy is to relieve symptoms of hypogonadism and preserve bone density. Testosterone is contraindicated if a testosterone-dependent neoplasm (e.g., prostate cancer), hyperviscosity, or sleep apnea is present. In adult men with hypergonadotropic hypogonadism and in men with hypogonadotropic hypogonadism not desiring fertility, testosterone therapy should be considered as first-line therapy. In hypogonadal men, testosterone therapy improves bone density, lean body mass, hemoglobin, energy levels, and sexual function with increases in prostate volume [97]. No improvement may be found in underlying depression [98]. HIV-positive hypogonadal men may have significant improvements in libido, energy levels, depression, and muscle mass [99]. In boys who have not gone through puberty, low doses of testosterone should be used with gradual increases, because aggressive behavior may occur [100].

Preparations of testosterone include testosterone enanthate or cypionate by intramuscular injection, transdermal testosterone by scrotal patch, transdermal testosterone patch through normal skin, and testosterone gel. Oral testosterone preparations should not be used because of poor potency and risk of hepatic injury. Intramuscular preparations of testosterone should be given every 7 to 14 days. Intramuscular injection of testosterone undecanoate is an attractive new therapy that can be administered quarterly. Monitoring of testosterone levels with the gel or patches can be done randomly and dosing adjusted to keep the level in the normal range, 300 to 1,000 pg/dl. For injections, the midpoint between-injections dose should be in the midnormal range. Improvement in clinical parameters should also be monitored, such as muscle mass, bone density, well-being, erectile function, and libido. Prostate size and prostate-specific antigen (PSA) should be monitored at least annually. If the PSA is above 4 ng/ml at outset or if it increases, referral of the patient to a urologist for possible ultrasound and biopsy is needed. For selected men, serial measurement of BMD during androgen therapy might be helpful to confirm end-organ effects. Although increasing testosterone levels in hypogonadal men with testosterone replacement may slightly increase PSA levels, the result is an increase from below normal into the normal range, with concomitant increase in prostate volume from subnormal to normal size, but with no increase in the frequency of prostate cancer. And, in hypogonadal men, treatment with testosterone did not significantly increase the incidence of prostate cancer over that expected for age. Hematocrit should be monitored to detect polycythemia [101]. Treatment of male infertility in men with hypogonadotropic hypogonadism is covered in the section on infertility.

TREATMENT OUTCOMES

A meta-analysis [102] of randomized placebo-controlled trials that measured the effect of testosterone use on sexual function in men with sexual dysfunction and varying testosterone levels reported that testosterone use in men with low initial testosterone levels was associated with small improvements in satisfaction with erectile function and moderate improvements in libido. The inconsistencies in response to testosterone therapy are due in part to the relative impact of other conditions common in elderly patients (e.g., chronic diseases such as diabetes, sleep apnea, depression, and cardiovascular disease) that may affect sexual function to a greater extent than any decline in androgen levels.

The effect of testosterone therapy on the cardiovascular system of older men has been addressed in several studies. The lack of cardiovascular risk in testosterone-treated older men has been supported by three meta-analyses [103–105]. The problem with meta-analyses assessment of cardiovascular risk is that none

of the available randomized controlled trials (RCTs) were designed to assess this outcome. These studies cannot be assessed as to the biases and confounding that occurred when adverse cardiovascular events were recorded or evaluated since cardiovascular health was not the primary outcome. However, a recent randomized control trial has raised concerns of increased cardiovascular events in testosterone-treated older men [106]. The men in the trial had high rates of chronic diseases such as diabetes and cardiovascular disease, and the treated group experienced significantly higher rates of cardiovascular events than the controls. Further studies are needed to address this issue.

INFERTILITY

Definition

A couple is considered infertile if they are unable to conceive after 12 months or more of unprotected intercourse in the absence of surgical sterility or contraception. Primary infertility refers to couples that have never had a pregnancy. Secondary infertility refers to couples having had a prior pregnancy.

Epidemiology

According to the National Center for Health Statistics, the estimated number of women aged 15 to 44 with infertility was 6.1 million, and the number seeking fertility services was 9.3 million in 2005 [107]. It affects 2 to 4 million couples and is classified as:

- Relative factors:
  - Delayed childbearing
  - Sexually transmitted diseases
  - Availability of successful treatment options (ART)
- Absolute infertility (sterility)
  - Absence of sperm (azoospermia)
  - Absence of oocytes (premature ovarian failure)
  - Absence of functional tubes
- Subfertility or relative infertility: reduced fertility potential

Etiology

In a study of 708 couples with infertility in England, the common causes of infertility were noted to be idiopathic (28% of cases), male factor (24%), ovulatory dysfunction (21%), tubal disease (14%), endometriosis (6%), sexual dysfunction (6%), or cervical defects or mucus problems (3%) [108]. About 15% to 20% of infertile couples have both male and female factors reducing fertility.

Evaluation

The initial evaluation of the infertile couple should include a semen analysis, evaluation of ovulation, and test of tubal patency (hysterosalpingogram [HSG]) in addition to a thorough history and physical examination.

The World Health Organization has established the parameters for fertile semen [109]. These include a count of greater than 20 million/ml and a motility of greater than 40% to 50%. The importance of sperm morphology in evaluating male fertility potential is controversial. Values below these are designated as subfertile but are still associated with pregnancy. The absence of sperm, azoospermia, is often associated with hypergonadotropic hypogonadism and is unresponsive to any treatment. However, sperm may be found by testicular aspiration and used in in vitro fertilization by means of intracytoplasmic sperm injection (ICSI). Genetic studies to assess for microdeletion of the Y chromosome should be considered.

Ovulatory function can be assessed by the menstrual history, basal body temperature charts, midcycle measurement of urinary LH ovulation kits [110], a midluteal progesterone level, or endometrial biopsy.

When ovulatory failure is diagnosed, an etiology should be determined. Studies should include an early follicular phase FSH to determine whether ovarian failure is present, a prolactin test to evaluate for hyperprolactinemia, and measurement of testosterone and DHEA-S levels to test for hyperandrogenism. Female infertility with ovulatory sufficiency should prompt an investigation of anatomic disease (e.g., tubal obstruction, uterine abnormalities, or endometriosis) assessed by ultrasound, hysterosalpingography, laparoscopy, and hysteroscopy, as clinically indicated.

The cervical factor can be assessed by a midcycle postcoital test wherein the presence and motility of sperm is assessed in cervical mucus aspiration after intercourse. If sperm are inactivated by the cervical mucus and they are motile without contact, a "cervical factor" may be operative. Although there is general disagreement regarding the interpretation of the postcoital test as a primary cause of infertility, dysmucorrhea is a common side effect of clomiphene therapy, and a poor postcoital test during treatment would raise the importance of intrauterine insemination (IUI) [111].

An HSG should be performed prior to treatment to assess tubal patency.

Treatment

Ovulation induction for the treatment of ovulatory dysfunction involves restoration of folliculogenesis by stimulating the production of gonadotropins or by injecting gonadotropins.

Clomiphene citrate [111] is the best initial treatment for the large majority of anovulatory infertile women. It alters pulsatile hypothalamic GnRH secretion to stimulate increased pituitary gonadotropin release that, in turn, drives ovarian follicular activity. Successful therapy requires monitoring of follicle growth to validate an adequate response through the use of ultrasonography and estradiol levels. If clomiphene treatment does not achieve adequate follicle development, then recombinant DNA–produced FSH with or without LH can be administered [112]. More than 80% of women will ovulate, although pregnancy rates can vary depending on many individual factors.

Treatment of male infertility should be directed at the underlying disorder. If a large varicocele is present, surgery may improve sperm counts and fertility rates [113]. Men with hypogonadotropic hypogonadism may respond to therapy with gonadotropins. Men with acquired disease may respond to hCG injections alone at 1,500 to 2,000 IU, three times a week, given intramuscularly or subcutaneously. Response to therapy, as measured by semen analysis, may take 6 to 12 months. In men with congenital hypogonadotropic hypogonadism, or those that due not respond to hCG alone, recombinant FSH in dose of 75 to 150 IU three times a week can be added to the hCG treatment [114]. Antiestrogen therapy with clomiphene citrate can improve testosterone levels in men, but in some studies, there was no significant effect on pregnancy rate [115], although a recent study with clomiphene and antioxidants [116] in men with idiopathic male factor found increased semen parameters and pregnancy rates. In men with low sperm counts, IUI can improve the chances for pregnancy over timed intercourse with natural cycles and with controlled ovarian hyperstimulation cycles [117]. ICSI with in vitro fertilization (IVF) is associated with significantly higher oocyte fertilization rates than is IVF alone in men with male factor infertility [118].

In unexplained infertility, defined as normal semen analysis, ovulatory cycles, and tubal patency by HSG, pregnancy rates with IVF are not significantly different than those from IUI with and without controlled hyperstimulation [119].

IVF is indicated if infertility from tubal disease is present or in male factor, especially when combined with ICSI. In the treatment of women with unexplained infertility, clomiphene citrate has been found to be effective based on randomized prospective trials with an odds ratio (OR) of 2.5 (95% CI, 1.35–4.62) [120]. In women with ovulatory dysfunction, clomiphene citrate is even more effective, with an OR of 3.41 (95% CI, 4.23–9.48) [121]. Risk of ovarian cancer, however, may be increased in women with infertility, although it is has not been directly linked with fertility medications [122]. For unexplained infertility, IUI combined with superovulation is more effective than IUI or intracervical insemination (ICI) with superovulation and, in turn, more effective than ICI alone [123].

As a final note, it is critical to discuss issues of age-related decrease in reproductive function in older women. The infertility rate is about 6% at age 20 to 24 years, about 9% at 25 to 29 years, about 15% at 30 to 34 years, about 30% at 35 to 39 years, and about 64% at 40 to 44 years. This time frame is associated with increasing miscarriage rates as monthly fecundability declines. Ovarian reserve, or reproductive potential, can be assessed by:

- Cycle day 3 FSH/estradiol (FSH < 15, estradiol < 50 pg/ml) [124]
- Antral follicle count
- Antimüllerian hormone
- Clomiphene challenge test [125]

At present antimüllerian hormone, produced by follicular granulosa cells, as a surrogate marker of follicular activity, may be the best predictor of ART success [126].

MENOPAUSE

Definition

Menopause (adult-onset ovarian failure) occurs after the last menstrual period, although symptoms may start much earlier. After 1 year of amenorrhea, menopause is likely and can be confirmed by an elevated FSH if needed. The average age of menopause is 51 years.

Diagnosis

Diagnosis can be confirmed by an elevated FSH level. If cycles are still present, perimenopausally, the early follicular phase FSH will be increased.

Treatment

The primary purpose of therapy is to relieve significant menopausal symptoms. The decision to treat must be individualized in light of the potential benefits and risks of hormone replacement therapy (HRT). Clear evidence exists that vasomotor symptoms are significantly relieved by HRT compared with placebo [127,128]. Vaginal dryness and urogenital atrophy are significantly improved by estrogen [128,129]. Urinary tract infections have improved in some studies [129,130], but no benefit on urinary tract infection was noted in the Heart and Estrogen/Progestin Replacement Study (HERS) study [131]. Depression in postmenopausal women may respond significantly to estrogen therapy, even in the absence of vasomotor symptoms [132,133], although only women with vasomotor symptoms improved in the HERS study [134]. Other potential benefits of menopausal hormone therapy (MHT) include prevention of bone loss and osteoporosis-related fracture and reduced risk of colorectal cancer. The issue of dementia prevention is still controversial because some studies suggest benefit, whereas no benefit and increased risk of cognitive impairment were found in the Women's Heath Initiative study [135–137].

Although observational trials such as the Nurses Health Study [138] reported a significant reduction in the risk of myocardial infarction in users of HRT, more

recent RCTs have not confirmed this benefit [139]. Reanalysis of the Women's Health Initiative data, however, suggests that the discrepancy may be explained by a differential effect of estrogen depending upon the age and time since menopause when HRT is used, with younger women perhaps showing benefit, with greater cardiovascular risk after the age of 70 [140,141]. HRT is currently not recommended for either primary or secondary prevention of heart disease. Ongoing studies may alter this recommendation in the future if significant benefit is shown. Other risks of MHT include an increased risk of thromboembolism and biliary tract disease [142].

The use of estrogen/progesterone combination therapy may be associated with a higher risk of breast cancer, greater node positivity, and a nonstatistically significant mortality in treated women, particularly with prolonged use [143,144]. Estrogen-alone therapy (appropriate for women with a previous hysterectomy) was not associated with this risk in the Women's Health Initiative Study [145]. The type of progesterone used may in fact influence outcome [146].

At present, recommendations are to use as low a dose of HRT as possible for treatment of significant vasomotor symptoms or vaginal dryness and for as brief a period as required. Alternatives for protection against osteoporosis and heart disease should be discussed. Small trials have been done showing some benefit for treatment of vasomotor symptoms with selective serotonin reuptake inhibitors, clonidine, megestrol, and gabapentin, but no comparison trials with estrogen have been conducted [143].

REFERENCES

Amenorrhea

1. (3) **Pittock ST** et al. Mayer-Rokitansky-Kuster-Hauser anomaly and its associated malformations. Am J Med Genet A 2005;135:314–316.

   Retrospective chart review of 25 patients between 1975 and 2002 found 20% scoliosis, 28% unilateral renal agenesis, 16% nonvertebral skeletal anomalies, and 44% vertebral anomalies; two had unilateral ovarian agenesis. Cardiac anomalies occurred in 16%, including truncus arteriosus, PDA, patent foramen ovale, and mitral valve disease.

2. (3) **Zenteno JC** et al. Molecular analysis of the anti-müllerian hormone, the anti-müllerian hormone receptor, and galactose-1-phosphate uridyl transferase genes in patients with the Mayer-Rokitansky-Kuster-Hauser syndrome. Arch Gynecol Obstet 2004;269:270–273.

   Fifteen patients with müllerian agenesis underwent molecular analysis of antimüllerian hormone and its receptor genes. No deleterious mutations were found. Although new polymorphisms were identified, they were not different between subjects and controls, making this an unlikely genetic cause of the syndrome.

3. (3) **Biason-Lauber A** et al. A WNT4 mutation associated with müllerian-duct regression and virilization in a 46,XX woman. N Engl J Med 2004;351:792–798.

   A single case report of a loss-of-function mutation in the WNT4 gene, which codes for a protein that suppresses male sexual differentiation and represses biosynthesis of gonadal androgens in females, was found in an 18-year-old with primary amenorrhea and absent müllerian-derived structures. This suggests that WNT4 is important in maintenance of the female phenotype.

4. (3) **Patsalis PC**. Detection and incidence of cryptic Y chromosome sequences in Turner syndrome patients. Clin Genet 1998;53:249–257.

   The presence of Y chromosome sequences in TS patients may predispose them to gonadoblastoma formation with an estimated risk of 15% to 25%. Fifty TS patients were screened for the presence of Y chromosome material by using a combination of polymerase chain reaction (PCR) and nested PCR followed by Southern blot analysis of three genes: the sex-determining region Y, testis-specific protein Y encoded, and RNA-binding motif protein (RBM) (previously designated as YRRM), and nine additional STSs spanning all seven intervals of the Y chromosome. Karyotypes were divided in four groups: five (23.8%) of the 21 TS patients that have the 45,X karyotype (group A) also have cryptic Y sequences; none of the seven patients who have karyotypes with anomalies on one of the X chromosomes have Y mosaicism (group B); one (6.3%) of the 16 patients with a mosaic karyotype has Y material (group C); and six (100%) of six patients with a supernumerary marker chromosome have Y chromosome sequences (group D).

5. (3) **Meyers CM**. Gonadal dysgenesis in 46 XX individuals: Frequency of the autosomal recessive form. Am J Med Genet 1996;63518–63524.

   Gonadal (ovarian) dysgenesis with normal chromosomes (46,XX) clearly is a heterogeneous condition. In some forms, the defect is restricted to the gonads, whereas other affected females show neurosensory hearing loss (Perrault syndrome). Nongenetic causes exist as well. To elucidate the proportion of XX gonadal (ovarian) dysgenesis due to autosomal recessive genes, the authors used segregation analysis of 17 published and 18 unpublished families having at least two female offspring. Analysis was restricted to cases in which ovarian failure was documented by the presence of streak ovaries (published cases) or elevated gonadotropins (unpublished cases). The segregation ratio estimate was 0.16, suggesting that many 46,XX females with gonadal (ovarian) dysgenesis represent a disorder segregating as an autosomal recessive trait, placing sisters of these cases at a 25% risk for this disorder.

6. (3) **Ogata T**. Short stature homeobox-containing gene duplication on the der(X) chromosome in a female with 45X/46,X,der(X), gonadal dysgenesis and tall stature. J Clin Endocrinol Metab 2000;85:2927–2930.

   Chromosomal analysis of the X chromosome of a Japanese female with 45,X[40]/46,X, der(X)[60], primary amenorrhea, and tall stature was performed. Fluorescence in situ hybridization analysis for 10 loci/regions on the X chromosome together with the whole X chromosome and the Xp-specific and Xq-specific paintings showed that the der(X) chromosome was associated with duplication of roughly distal half of Xp, including SHOX (short stature homeobox-containing gene), and deletion of most of Xq. The authors suggest that the tall stature of this female is caused by the combined effects of SHOX duplication on the der(X) chromosome and gonadal estrogen deficiency. They note that the similarity in the growth pattern between this female and patients with estrogen resistance or aromatase deficiency implies that the association of an extra copy of SHOX with gonadal estrogen deficiency may represent another clinical entity presenting as tall stature resulting from continued growth in late teens or into adulthood.

7. (2) **Sarpel U** et al. The incidence of complete androgen insensitivity in girls with inguinal hernias and assessment of screening by vaginal length measurement. J Pediatr Surg 2005;40:133–136.

   A prospective study of prepubertal girls with inguinal hernias revealed an incidence of complete androgen insensitivity syndrome (CAIS) of 1.1% in these girls, with short vaginal length being a marker for suspicion of the syndrome.

8. (3) **Ledig S** et al. Novel and recurrent mutations in patients with androgen insensitivity syndromes. Horm Res 2005;63:263–269.

   Twenty-four patients with AIS were studied by sequencing androgen-receptor gene. Nineteen of the investigated patients were affected by CAIS, and five had partial androgen insensitivity syndrome. Twelve unreported mutations were found, as well as nine recurrent mutations (three recurrent mutations were detected twice) in exons 2 to 8 of the androgen-receptor gene. Apart from truncating mutations, a reliable genotype–phenotype correlation cannot be established. Therefore, modifying factors must be effective.

9. (3) **Quinton R** et al. Idiopathic gonadotropin deficiency: Genetic questions addressed through phenotypic characterization. Clin Endocrinol 2001;55:163–174.

   A clinical study of 170 male and 45 female IHH patients. Eighty percent of data were obtained from case records, and 20% were collected prospectively. Parameters assessed included olfaction, testicular volume, family history of hypogonadism, anosmia or pubertal delay, and history or presence of testicular maldescent or neurologic, renal, or craniofacial anomalies. Olfactory acuity was bimodally distributed. Testicular volume, a marker of integrated gonadotropin secretion, did not differ significantly between anosmic and normosmic patients. The prevalence of cryptorchidism was nearly three times greater in anosmic (70.3%, of which 75.0% are bilateral) than in normosmic (23.2%, of which 43.8% are bilateral) patients. Disorders of eye movement and hearing occurred only in association with KS. The findings revealed a clear phenotypic separation between KS and nIHH. Pedigree studies suggest that autosomal KS is a heterogeneous condition, with incomplete phenotypic penetrance within pedigrees, and that some cases of autosomal KS, nIHH, and isolated anosmia may have a common genetic basis. Most sporadic KS cases are presumed to have an autosomal basis.

10. (4) **Conway GS**. Premature ovarian failure and FMR1 gene mutations: An update. Ann Endocrinol (Paris) 2010;71(3):215–217.

    Review article noting the mandate for screening for fragile X permutations as standard of care in evaluation of POF. There is a 5% chance of conception in this group, greater in the FRAXA permutation subgroup. Thus, these women are at risk of having a child with fragile X syndrome. Genetic counseling and identification of female relatives may reveal other family members at risk for transmitting the fragile X syndrome.

11. (4) **Ferreira SI** et al. X-chromosome terminal deletion in a female with premature ovarian failure: Haploinsufficiency of X-linked genes as a possible explanation. Mol Cytogenet 201020;3:14.

A POF patient with a 46,X,del(X)(q26) karyotype and with skewed X chromosome inactivation of the structural abnormal X chromosome was reported. Despite the hemizygosity of *FMR1* gene, the fragile X syndrome is not present since the normal X chromosome is not subject to methylation. The described deletion supports the hypothesis that haploinsufficiency of X-linked genes can be the basis of POF. The authors emphasize that "special attention should be paid to X-linked genes in region Xq28 since they escape inactivation and might have a role in this disorder."

12. (3) **Dolzan V** et al. Mutational spectrum of steroid 21-hydroxylase and the genotype-phenotype association in Middle European patients with congenital adrenal hyperplasia. Eur J Endocrinol 2005;153:99–106.

The molecular genetic basis of 21-hydroxylase deficiency is clearly demonstrated in this large-scale study in a European registry. By genotyping for the most common point mutations, CYP21 gene deletion/conversion and the 8-bp deletion in exon 3, it was possible to identify the mutation in 94% to 99% of the diseased alleles in this population. Steroid 21-hydroxylase (CYP21) and the genotype–phenotype correlation were assessed in 432 patients with CAH and 298 family members of middle European ancestry. CYP21 gene deletion and In2 and Ile172Asn mutation accounted for 72.7% of the affected alleles in the whole study group. A good genotype–phenotype correlation was observed, with the exception of Ile172Asn and Pro30Leu mutations. In 37% of patients, low-resolution genotyping could not identify the causative mutation or distinguish homozygosity from hemizygosity. With high-resolution genotyping, the causative mutations could be identified in 341 of 348 analyzed patients. A novel mutation Gln315Stop was found in one simple virilizing CAH (SV-CAH) patient. In the remaining seven patients, polymorphisms were identified as the leading sequence alteration. In patients with a mild form of the disease and no detectable mutation, CYP21 gene polymorphisms should be considered as a plausible disease-causing mutation. The presence of elevated basal and ACTH-stimulated 17-hydroxyprogesterone, premature pubarche, advanced bone age, and clitoral hypertrophy directly implicated Asn493Ser polymorphism in the manifestation of nonclassic (NC)- and SV-CAH.

13. (3) **King JA** et al. Long term corticosteroid replacement and bone mineral density in adult women with classical congenital adrenal hyperplasia. J Clin Endocrinol Metab 2006;91(3):865–869.

The risk of overtreatment of adrenal hyperplasia was demonstrated in this observational study of 11 women with salt-losing (SL) CAH and 15 with the SV 21-hydroxylase deficiency who underwent DEXA measurement of spine and whole-body bone density and compared with 9 unaffected sisters as controls. Osteopenia was noted in 45% of SL, 13% of SV, and 11% of controls. Lumbar spine and whole-body BMDs of CAH subjects were lower than those of controls. CAH patients with osteopenia had lower levels of DHEA-S and DHEA compared with similar patients with normal bone density. Adrenal androgen levels were particularly suppressed among postmenopausal women receiving glucocorticoid replacement. Oversuppression of adrenal androgens is associated with increased risk for bone loss in this population.

14. (2) **Rivkees SA, Crawford JD**. Dexamethasone treatment of virilizing congenital adrenal hyperplasia: The ability to achieve normal growth. Pediatrics 2000;106:767–773.

Long-acting steroid suppression with dexamethasone resulted in favorable growth patterns and appropriate timing of puberty. The use of dexamethasone at a dose of 0.27 ± 0.01 mg/m^2/d in 17 boys and 9 girls with SV-CAH over approximately 7 years resulted in a final AH comparable to estimated midparental height in 9 boys and 6 girls. The seven children who were started on therapy with more advanced bone age had shorted predicted/FHs, although these improved during the course of therapy. During treatment, 17-ketosteroid excretion rates were normal for age, and 17-hydroxyprogesterone values were 69.6 ± 18 ng/dl. Testicular enlargement was first detected at 10.7 ± 0.8 years.

15. (4) **Cobin RH** et al.; Writing Committee. American Association of Clinical Endocrinologists Position Statement on metabolic and cardiovascular consequences of polycystic ovary syndrome. Endocr Pract 2005;11(2):125–134.

16. (3) **Manuel M** et al. The age of occurrence of gonadal tumors in intersex patients with a Y chromosome. Am J Obstet Gynecol 1976;124:293–300.

A retrospective study of 320 cases of gonadal dysgenesis, asymmetric gonadal differentiation, and male hermaphrodites demonstrated a significant increase in gonadal tumors shortly after puberty. Testicular feminization patients had a lower risk of 3.6% up to age 25. In testicular feminization, it may be acceptable to wait until after puberty, although gonads should be removed on diagnosis in Y chromosome–containing disorders.

17. (4) **Saenger P** et al. Recommendations for the diagnosis and management of Turner syndrome: Fifth International Symposium on Turner Syndrome. J Clin Endocrinol Metab 2001;86:3061–3069.

Comprehensive recommendations on the diagnosis of TS and the care of affected patients were published in 1994. In the light of recent advances in diagnosis and treatment of TS, an international multidisciplinary workshop was convened in March 2000 to update these recommendations. This article details the outcome of this workshop, describing the genetics and diagnosis of the syndrome and presenting practical treatment guidelines.

18. (2) **Swerdlow AJ** et al. Mortality and cancer incidence in persons with numerical sex chromosome abnormalities: A cohort study. Ann Hum Genet 2001;65:177–188.

This cohort observational study included 400 patients with TS and 8,609 person-years of follow-up. The RR of death was high at 4.1, with deaths from aortic aneurysm having a RR of 63.2. Other congenital abnormalities were also noted.

19. (1) **Sas TC** et al. Normalization of height in girls with Turner syndrome after long-term growth hormone treatment: Results of a randomized dose-response trial. J Clin Endocrinol Metab 1999;84:4607–4712.

This was a randomized trial of 68 girls aged 2 to 11 with TS randomly assigned to one of three doses of GH. Estradiol was added at the age of 12, and follow-up was continued until FH occurred. A normal range of AH was achieved in 85%, with an estimated gain of about 4 in the higher dose groups after an average of about 7 years of GH use.

20. (1) **Chernausek SD** et al. Growth hormone therapy of Turner syndrome: The impact of age of estrogen replacement on final height: Genentech, Inc, Collaborative Study Group. J Clin Endocrinol Metab 2000;85:2439–1245.

This was a RCT of estrogen plus GH in girls with TS. At entry, the girls were all younger than 11 years, with a mean age of 9.5 years. Estrogen was either added at age 12 or at age 15. The height gain in girls begun on estrogen at age 15 was 8.4 ± 4.3 cm and the height gain in girls started on estrogen at age 12 was only 5.1 ± 3.6 cm ($p < 0.01$). FH was most dependent on number of years of GH therapy before starting estrogen.

21. (2) **Reiter EO** et al. Early initiation of growth hormone treatment allows age-appropriate estrogen use in Turner's syndrome. J Clin Endocrinol Metab 2001;86:1936–1941.

A population of 344 girls with TS followed up in the National Cooperative Growth Hormone Study database was assessed for GH and estrogen therapy in relation to FH. In girls started on GH early, greater gains in height were shown despite estradiol therapy. If estrogen is needed because of behavioral issues, then early treatment with GH can help preserve FH.

22. (1) **Ross JL** et al. Effects of estrogen on nonverbal processing speed and motor function in girls with Turner's syndrome. J Clin Endocrinol Metab 1998;83:3198–3204.

This was a double-blind randomized control trial demonstrating that motor skills in 10- to 12-year-old girls with TS were significantly improved with estrogen therapy.

23. (4) **Bouchlariotou S** et al. Turner's syndrome and pregnancy: Has the 45,X/47,XXX mosaicism a different prognosis? Own clinical experience and literature review. J Matern Fetal Neonatal Med 2011;24(5):668–672.

A 33-year-old woman with a mosaic Turner syndrome karyotype 45,X/47,XXX who conceived spontaneously and had two successful pregnancies was presented. Her only manifestation of Turner syndrome was short stature. The authors note that spontaneous puberty occurs in fewer than 10% of Turner syndrome (mosaic) patients and that although pregnancy is possible, it carries a high risk of fetal loss and chromosomal and congenital mutations.

24. (4) **Cabanes L** et al. Turner Syndrome and Pregnancy: Clinical Practice. Recommendations for the Management of Turner Syndrome before and during Pregnancy. Eur J Obstet Gyn Reprod Biol 2010;152(1):18–24.

A French expert panel reviews potential complications of pregnancy and recommends appropriate standards of care for prenatal evaluation, contraindications to pregnancy, and appropriate antenatal care, delivery, and postnatal follow-up.

25. (1) **van Kasteren YM** et al. Premature ovarian failure: A systematic review on therapeutic interventions to restore ovarian function and achieve pregnancy. Hum Reprod Update 1999;5:483–492.

Meta-analysis of seven controlled trials with a total of 194 women with premature ovarian failure assessed for ovulatory status and pregnancy in response to various interventions. Interventions included gonadotropins (e.g., human menopausal gonadotropin), estrogen, growth hormone, GnRH agonists and antagonists, danazol, clomiphene, birth control pills, and glucocorticoids. None of the treatments increased the rate of ovulation or pregnancy with an expected basal pregnancy rate of 5% to 10%.

26. (2) **Hogler W** et al. Importance of estrogen on bone health in Turner syndrome: A cross-sectional and longitudinal study using dual-energy X-ray absorptiometry. J Clin Endocrinol Metab 2004;89:193–199.

Eighty-three patients with TS age 4 to 24 were followed longitudinally with DEXA. In subjects who remained prepubertal, bone density decreased, whereas it increased in subjects entering puberty with hormonal therapy.

27. (3) **Bakalov VK** et al. Bone mineral density and fractures in Turner syndrome. Am J Med 2003;115:259–264.

Areal bone density corrected for skeletal size in 40 women with estrogen-treated TS was compared with that in 40 age-matched healthy women. Structured personal interviews were used for the determination of fracture and estrogen use. Bone density was measured in subjects and control. The prevalence of osteoporosis and fractures was similar in both groups. Women shorter than 150 cm are more likely to be misdiagnosed with osteoporosis when areal bone density is measured unless adjusted for height. This study indicates that the historical observation of osteoporosis and fractures in untreated TS can be compared with a favorable prognosis with the use of estrogen.

28. (3) **Hanton L** et al. The importance of estrogen replacement in young women with Turner syndrome. J Womens Health (Larchmt) 2003;12:971–977.

Structured personal interview was used to determine estrogen use, and spine BMD was measured by DEXA and QCT in 30 women with Turner syndrome, ages 30 to 59 years. Thirty-four subjects had received HRT according to guidelines, whereas the rest had not. The untreated group had a reduced spine QCT by 20%, with 6 of 16 with osteoporosis and 3 of 16 having vertebral fractures as compared with none of 34 in the treated group.

29. (3) **Gravholt CH** et al. Increased fracture rates in Turner's syndrome: A nationwide questionnaire survey. Clin Endocrinol (Oxf) 2003;59:89–96.

A previous registry study of TS patients revealed an increased risk of osteoporosis and fractures. In this study, 322 patients in Denmark were compared with 1,888 controls matched for age and geographic region by questionnaire. Of the patients with TS, 71% had taken HRT beginning at a mean of 16 years of age, and 16% had used growth hormone. The hazard risk for fracture in the Turner group was 1.35 (CI, 1.04–1.75; $p < 0.03$) with time to first fracture age 53 in TS versus 63 years in controls. This study did not correlate the use of HRT/GH with fractures among the subgroups with Turner syndrome.

30. (*3*) **Costa AM** et al. Bone mineralization in Turner syndrome: A transverse study of the determinant factors in 58 patients. J Bone Miner Metab 2002;20:294–297.

Fifty-eight patients with TS were studied with DEXA; 86% had z scores less than −1 SD, and 46% had z scores less than −2.5 SD. BMD was negatively correlated with age and height and positively correlated with weight and BMD. A higher BMD was observed in those who used hormone replacement for a longer period.

31. (3) **Benetti-Pinto CL** et al. Factors associated with the reduction of bone density in patients with gonadal dysgenesis. Fertil Steril 2002;77:571–575.

Thirty-eight women, aged 16 to 35 years (mean, 24.6 years) with TS or pure gonadal dysgenesis were studied with DEXA, and variables associated with BMD were evaluated by multiple linear regression analysis: 90% had osteopenia or osteoporosis of the spine, and 55% in the femoral neck. The length of estrogen therapy and the BMI showed a positive association with BMD at the lumbar spine and femoral neck.

32. (4) **Speiser PW** et al; Endocrine Society. Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: An Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2010;95(9):4133–4160.

An expert panel reviews clinical, biochemical, and molecular diagnosis of CAH and current evidence-based opinion regarding management of both classical and nonclassical CAH in children, adults, and pregnancy.

33. (3) **Grinspoon S** et al. Prevalence and predictive factors for regional osteopenia in women with anorexia nervosa. Ann Intern Med 2000;21:33:790–794.

DEXA of the spine and femoral neck was measured in 130 women with anorexia nervosa. BMD was reduced by at least 1.0 SD at one or more skeletal sites in 92% of patients and by at least 2.5 SD in 38% of patients. Weight was the most consistent predictor of BMD at all skeletal sites. Twenty-three percent of patients were current estrogen users, and 58% were previous estrogen users. BMD did not differ by history of estrogen use at any site. Weight, but not estrogen use, is a significant predictor of BMD in this population at all skeletal sites.

34. (3) **Miller KK** et al. Preservation of neuroendocrine control of reproductive function despite severe undernutrition. J Clin Endocrinol Metab 2004;89:4434–4438.

In total, 116 women were studied: 42 low-weight women who fulfilled all DSM4 diagnostic criteria for AN, except for amenorrhea; and 74 women with AN and amenorrhea for at least 3 months. The two groups were similar in BMI, percentage ideal body weight, duration of eating disorder, age of menarche, and exercise. Eumenorrheic patients had a higher mean estradiol level than did amenorrheic subjects. Mean percentage body fat, total body fat mass, and truncal fat were higher in eumenorrheic than amenorrheic patients. The mean leptin level and IGF-1 levels were higher in the eumenorrheic than in the amenorrheic group. Only minor differences in severity of eating disorder symptoms were seen, as measured by the Eating Disorders Inventory, and where differences were observed, eumenorrheic subjects manifested more severe symptoms than did amenorrheic subjects. Mean BMDs at the spine were low in both groups but were higher in patients with eumenorrhea than in those with amenorrhea, but menstrual function was not protective at the hip. It was concluded that fat mass may be important for preservation of normal menstrual function in severely undernourished women, and this may be in part mediated through leptin secretion, and that nutritional intake and normal hormonal function may be independent contributors to maintenance of trabecular bone mass in low-weight women.

35. (1) **Grinspoon S** et al. Effects of recombinant human IGF-I and oral contraceptive administration on bone density in anorexia nervosa. J Clin Endocrinol Metab 2002;87:2883–2891.

    In a blinded, placebo-controlled study, 60 osteopenic women with anorexia nervosa, ages 18 to 38 years, BMI (17.8 ± 0.3 kg/m^2) and spinal BMD T score (-2.1 ± 0.1 SD), were randomized to receive either recombinant IGF-1 and OCP, OCP alone, IGF-1 alone, or no therapy for 9 months. All subjects received calcium, 1,500 mg/d, and a standard multivitamin containing 400 IU of vitamin D. The rhIGF-1 was titrated to maintain IGF-1 levels within the age-adjusted normal range for each patient. Spine BMD increased significantly in response to rhIGF-1 and all rhIGF-1 groups versus all placebo treated, by analysis of covariance. OCP alone did not improve BMD over placebo but increased to the greatest extent in the combined treatment group compared with placebo-treated patients. The data indicate that osteopenic women with anorexia nervosa treated with rhIGF-1 showed more beneficial changes in bone density, compared with patients not treated with rhIGF-1. OCP therapy alone is not sufficient to improve bone density in undernourished patients but may augment the effects of rhIGF-1 in a combined treatment strategy.

36. (2) **Misra M** et al. Effects of rhIGF-1 administration on surrogate markers of bone turnover in adolescents with anorexia nervosa Bone. 2009;45(3):493–498.

    Recombinant IGF-1 was administered at a dose of 30 to 40 mg/kg twice daily to 10 consecutive girls with AN 12 to 18 years old, and 10 age-matched AN girls were followed without treatment for 7 to 9 days. PINP (a marker of bone formation) increased and CTX (a marker of bone resorption did not change) in treated subjects. No changes occurred in controls; rhIGF-1 was well tolerated without hypoglycemia. Short-term administration of rhIGF-1 causes an increase in a surrogate bone formation markers in girls with AN without significant side effects.

37. (3) **Lawson EA** et al. Hormone predictors of abnormal bone microarchitecture in women with anorexia nervosa. Bone 2010;46(2):458–463.

    A cross-sectional study of 23 women (12 with AN and 11 healthy controls) to determine hormonal predictors of trabecular bone microarchitecture. Bone microarchitectural measures, including apparent (app.) bone volume fraction, app. trabecular thickness, and app. trabecular number, were reduced ($p < 0.03$), and app. trabecular spacing was increased ($p = 0.02$) in AN versus controls. Decreased structural integrity at the ultradistal radius was associated with decreased BMD at all sites ($p \leq 0.05$) except for total hip. IGF-1, leptin, testosterone, and free testosterone levels predicted bone microarchitecture and were significant even controlling for BMI.

Hyperandrogenism and PCOS

38. (4) **Rosenfield RL, Deplewski D**. Role of androgens in the developmental biology of the pilosebaceous unit. Am J Med 1995;98(suppl 1A):80S–88S.

39. (3) **Cobin RH**. The case of the Elusive Androgen. Endocrine Practice 2002;8(6):433–438.

    A case report and review of the literature indicating that more serious disorders such as adrenal and ovarian tumors and hyperthecosis ovarii are usually associated with more severe elevations of androgen levels and correspondingly worse clinical hirsutism and virilization

40. (3) **Borgia F** et al. Correlation between endocrinological parameters and acne severity in adult women with acne. Acta Derm Venereol 2004;84:201–204.

    This study evaluated the relationship between clinical features, ultrasonographic data on polycystic ovaries, and hormonal parameters in 129 women more than 17 years of age with acne. Serum levels of androgens of ovarian and adrenal origin were measured. Menstrual cycle

regularity, hirsutism, BMI, and ultrasonographic evaluation of ovaries were recorded. Raised levels of at least one androgen were evident in a majority of our patients

41. (2) **Timpatanapong P, Rojanasakul A**. Hormonal profiles and prevalence of polycystic ovary syndrome in women with acne. J Dermatol 1997;24:223–229.

    The purpose of this study was to determine the hormonal profiles of women with acne and the prevalence of PCOS in women attending the dermatologic clinic with acne problems. There were 51 women with acne; 20 regularly menstruating volunteers without acne served as a control group. PCOS was found in 19 out of 51 patients with acne (37.3%) and none in the control group. Twenty acne patients had abnormal menstruation (39.2%). Acne cases had higher mean levels of serum total testosterone (T), free T, DHEA-S, and prolactin (PRL).

42. (2) **Cela E** et al. Prevalence of polycystic ovaries in women with androgenic alopecia. Eur J Endocrinol 2003;149:439–442.

    Eighty-nine women of mixed ethnic origin with androgenic alopecia were compared to seventy-three control women. A detailed history was taken, anthropometry was performed, and assessment of body-hair distribution was made. The presence of polycystic ovary (PCO) was established by pelvic ultrasound scan. Serum gonadotropins, testosterone, androstenedione, dihydrotestosterone, and SHBG concentrations were measured. Women with alopecia had a higher prevalence of PCO and hirsutism than the control population (PCO, 67% vs. 27%, $p < 0.00001$; hirsutism, 21% vs. 4%, $p < 0.003$). Women with alopecia (with or without PCO) had higher testosterone, androstenedione, and free androgen index than controls, even though few had frankly abnormal androgens.

43. (2) **Knochenhauer ES** et al. Prevalence of the polycystic ovary syndrome in unselected black and white women of the southeastern United States: A prospective study. J Clin Endocrinol Metab 1998;3:3078–3082.

    In a prospective study of 369 women, hirsutism was present in 2% to 8%, and PCOS, in 3.5% to 11.2%.

44. (2) **Azziz R** et al. The prevalence and features of the polycystic ovary syndrome in an unselected population. J Clin Endocrinol Metab 2004;89:2745–2749.

    Four hundred unselected consecutive premenopausal women (18–45 years of age) seeking a preemployment physical at the University of Alabama at Birmingham were studied (223 black, 166 white, and 11 of other races). Evaluation included a history and physical examination, a modified Ferriman-Gallwey hirsutism score, and serum screening for hyperandrogenemia, hyperprolactinemia, and 21-hydroxylase-deficient nonclassical adrenal hyperplasia. PCOS was diagnosed by the presence of the following: (1) oligoovulation, (2) hyperandrogenemia and/or hirsutism (modified Ferriman-Gallwey score >6), and (3) the exclusion of related disorders. The cumulative prevalence of PCOS in our population was 6.6% (26.5 of 400), including 15 subjects among the 347 women completing their evaluation and a calculated prevalence of 11.5 subjects among the remainder. The prevalence rates of PCOS for black and white women were 8.0% and 4.8%, respectively, not significantly different.

45. (4) **Azziz R** et al. Task force on the phenotype of the polycystic ovary syndrome of the androgen excess and PCOS Society. Fertil Steril 2009;91:456–88.

46. (2) **Polson DW** et al. Polycystic ovaries: A common finding in normal women. Lancet 1988;331:870–872.

    Two hundred fifty-seven normal women of reproductive age without menstrual disturbances, infertility, or hirsutism underwent pelvic ultrasound. Twenty-three percent were found to have polycystic ovaries.

47. (2) **Legro RS** et al. Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome: A prospective, controlled study in 254 affected women. J Clin Endocrinol Metab 1999;84:165–169

    Two-hundred fifty-four PCOS women, aged 14 to 44 years, were prospectively evaluated with a 75-g oral glucose challenge. The prevalence of glucose intolerance was 31.1% impaired glucose intolerance and 7.5% diabetes. PCOS women are at significantly increased risk for IGT and type 2 DM at all weights and at a young age.

48. (2) **Dunaif A**. Insulin action in the polycystic ovary syndrome. Endocr Metab Clinics North Am 1999;28(2):341–359.

    Glucose tolerance and insulin responses were evaluated in hyperandrogenemic women stratified on the basis of ovulation. Only women with chronic anovulation and hyperandrogenemia without secondary causes had basal or glucose-stimulated hyperandrogenemia or both, indicating the presence of insulin resistance. Subsequent studies have confirmed that insulin resistance is limited to women with the PCO morphology and chronic anovulation. Thus, insulin resistance is a unique feature of the syndrome of chronic anovulation and hyperandrogenemia.

The importance of insulin resistance in the pathogenesis of anovulation has recently been confirmed by studies of insulin-sensitizing drugs that restore ovulation in PCOS.

49. (4) **Grundy SM** et al. Diagnosis and management of the metabolic syndrome. Circulation 2005;112;e285–e290

50. (2) **Legro RS** et al. Changes in glucose tolerance over time in women with polycystic ovary syndrome: A controlled study. J Clin Endocrinol Metab 2005;90:3236–3242.

    A study to access the changes in glucose tolerance over time in a group of women with polycystic ovary syndrome (PCOS) (n = 71) and control women (n = 23) with regular menstrual cycles and baseline normal glucose tolerance (NGT). In the PCOS group, 25 (37%) had IGT and 7 (10%) had type 2 DM at baseline, compared with 30 (45%) and 10 (15%), respectively, at follow-up. The effect of PCOS, given NGT at baseline, is more pronounced with 16% conversion to IGT per year. This study supports that women with PCOS (especially with NGT) should be periodically rescreened for diabetes due to worsening glucose intolerance over time.

51. (2) **Dunaif A** et al. Acanthosis nigricans, insulin action, and hyperandrogenism: Clinical, histological, and biochemical findings. J Clin Endocrinol Metab 1991;73:590–595.

    This study was performed to determine the actual histologic prevalence of acanthosis nigricans and its relationship to sex hormone levels and insulin action. Insulin-mediated glucose disposal was determined by the euglycemic clamp technique, and neck or axillary skin biopsies were graded blind for the presence and severity of AN in lean and obese women with the PCOS and in age- and weight-matched normal ovulatory controls. AN was present on histologic examination in 13 of 13 obese PCO, 5 of 6 lean PCO, 13 of 14 obese normal, and 1 of 4 lean normal women. The severity of histologic AN was most highly correlated with insulin-mediated glucose disposal ($r = -0.61$; $p < 0.001$) rather than fasting ($r = 0.46$; $p < 0.05$) or glucose-stimulated insulin levels ($r = 0.48$; $p < 0.01$).

52. (4) **Rosner W** et al. Position statement: Utility, limitations, and pitfalls in measuring testosterone: An Endocrine Society position statement. J Clin Endocrinol Metab 2007;92:405–413

53. (2) **Steinberger E** et al. Utilization of commercial laboratory results in management of hyperandrogenism in women. Endocr Pract 1998;4:1–10.

    A review of testosterone levels from 17 studies of 649 total normal women demonstrated a mean testosterone level of 32.6 ± 2.7 ng/dl with a 95% CI of 22.1 to 33. The average weighted mean testosterone level in women with symptoms of hyperandrogenism in 14 studies of 996 patients was 62.1 ± 3.2 ng/dl (95% CI, 55.5–68.7). With a typical upper limit of testosterone of 90 to 95 ng/dl in commercial laboratories, most patients with hyperandrogenism are not diagnosed with elevated testosterone levels. An upper limit of 40 ng/dl is recommended.

54. (3) **Ayala C** et al. Serum testosterone levels and reference ranges in reproductive-age women. Endocr Pract 1999;5:322–329.

    The authors performed a cross-sectional retrospective study of 271 reproductive-age women encountered at an endocrinology clinic for complaints of potential thyroid problems. They had no clinical signs of hyperandrogenism and had not used oral contraceptives or glucocorticoids. The serum testosterone level in women with no acne, hirsutism, or menstrual dysfunction was 14.1 ± 0.9 ng/dl (mean ± standard error of the mean) (95% CI, 12.4–15.8). This group was considered our study reference population. In women with menstrual dysfunction but no acne or hirsutism, the mean testosterone level was significantly higher (17.9 ± 1.1 ng/dl; 95% CI, 15.7–20.0; $p < 0.002$); with mild hirsutism, it further increased (38.4 ± 5.1 ng/dl; 95% CI, 27.4–49.4; $p < 0.005$); and with moderate to severe hirsutism, it was still higher (49.0 ± 2.3 ng/dl; 95% CI, 44.4–53.6; $p < 0.003$). Serum DHEA-S levels showed similar patterns. The upper limit (mean ± 2 standard deviations) of testosterone in our study reference population was 28 ng/dl, a level that provided a sensitivity of 84% for detecting hyperandrogenemia. The authors comment that detection of hyperandrogenemia is essentially impossible when the upper limit of the reference range for testosterone from commercial laboratories (95 ng/dl) is used and suggest a reassessment of the normal range in reference laboratories.

55. (3) **Pasquali R** et al. Clinical and hormonal characteristics of obese amenorrheic hyperandrogenic women before and after weight loss. J Clin Endocrinol Metab 1989;68: 173–179.

    A group of obese hyperandrogenic amenorrheic women were studied to determine the effects of weight loss on anthropometry, hormonal status, menstrual cycles, ovulation, and fertility. All women ate a hypocaloric diet for a period of 8.0 ± 2.4 months. Weight loss ranged from 4.8 to 15.2 kg (mean, 9.7 ± 3.1 kg; 1.35 ± 0.56 kg/mo) and the waist to hip ratio, which was used as a measurement of body fat distribution, decreased from 0.86 ± 0.1 to 0.81 ± 0.06 ($p < 0.0001$). The women's mean plasma testosterone and LH concentrations decreased significantly ($p < 0.001$ and $p < 0.005$, respectively). A significant positive correlation was found

between the decreases in plasma testosterone levels and the decreases in glucose-stimulated insulin levels. Eight women had significantly improved menstrual cyclicity (responders), while twelve did not (nonresponders). The clinical characteristics and hormone values were similar in responder and nonresponder women.

56. (2) **Hoffmann R**. A 4-month, open-label study evaluating the efficacy of eflornithine 11.5% cream in the treatment of unwanted facial hair in women using TrichoScan. Eur J Dermatol 2008;18(1):65–70.

57. (2) **Guido M**. Drospirenone for the treatment of hirsute women with polycystic ovary syndrome: A Clinical, Endocrinological, Metabolic Pilot Study. J Clin Endocrinol Metab 2004;89(6):2817–2823.

    The aim of this study was to investigate the effects of the new estroprogestinic containing the antimineralcorticoid progestogen drospirenone (DRSP) in women with PCOS. Fifteen hirsute PCOS patients were treated with 30 μg ethinyl estradiol plus 3 mg DRSP for 12 cycles. Hirsutism significantly improved from the sixth cycle onward. Body weight and fat distribution as well as blood pressure remained stable throughout the treatment. Plasma levels of LH, testosterone, SHBG, and, consequently, the free androgen index significantly fell from the third cycle on.

58. (2) **Korytkowski M** et al. Metabolic effects of oral contraceptives in women with polycystic ovary syndrome. J Clin Endocrinol Metab 1995;80:3327.

    To study the effect of oral contraception on insulin sensitivity and lipids, 9 women with PCOS and 10 age- and weight-matched control women were studied before and during the third month of therapy with a low-dose norethindrone-containing triphasic combination OC using the hyperglycemic clamp technique. At baseline, the PCOS group had higher androgen, triglyceride, and glycosylated hemoglobin concentrations, with a greater insulin response to oral glucose and a lower insulin sensitivity index (ISI) than controls. During OC therapy, a reduction in ISI was observed in both groups, whereas an increase in triglycerides was observed only in controls, removing any observed difference between the two groups in ISI or lipids. In women with PCOS, an increase in insulin concentrations during hyperglycemia accounted for the decline in ISI ($p = 0.026$), whereas in control women, the decrease in ISI was attributable to a decrease in glucose disposal ($p = 0.004$).

59. (1) **Farquhar C** et al. Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne (Cochrane Review). In: The Cochrane Library. 3rd ed. Oxford: Update Software, 2002.

    All known RCTs of spironolactone compared with placebo were identified. After study evaluation, six small trials were further reviewed. Spironolactone at 100 mg daily resulted in statistically significant decreases in hair growth and lower Ferriman-Gallwey scores after 6 months. No clear effect on acne was noted.

60. (2) **Moghetti P** et al. Comparison of spironolactone, flutamide, and finasteride efficacy in the treatment of hirsutism: A randomized, double-blind, placebo-controlled trial. J Clin Endocrinol Metab 2000;85:89–94.

    This trial observed 40 hirsute women with a mean age of 20.4 years for 6 months taking placebo, spironolactone (100 mg), flutamide (250 mg), or finasteride (5 mg). After 6 months, the patients receiving active medications all demonstrated significant improvement with no significant difference between the treatment groups. About a 30% reduction in hirsutism score was observed compared with placebo ($p < 0.01$).

61. (1) **Pazos F** et al. Prospective randomized study comparing the long-acting gonadotropin-releasing hormone agonist triptorelin, flutamide, and cyproterone acetate, used in combination with an oral contraceptive, in the treatment of hirsutism. Fertil Steril 1999;71:122–128.

    This prospective randomized trial of 39 hirsute women compared GnRHa, cyproterone acetate, and flutamide in combination with a birth control pill over a 9-month period. Although all drugs were effective, the Ferriman-Gallwey scores demonstrated the most rapid response at 3 months with flutamide and cyproterone acetate. The most reduction was seen in the flutamide group by 9 months.

62. (1) **Muderris I** et al. A prospective, randomized trial comparing flutamide (250 mg/d) and finasteride (5 mg/d) in the treatment of hirsutism. Fertil Steril 2000;73:984–987.

    This is a randomized prospective study of 70 hirsute women observed for 1 year randomized to either flutamide, 250 mg daily, or finasteride, 5 mg daily. The hirsutism score for flutamide went from 17.8 at baseline to 4.8 at 12 months, a 71% reduction ($p < 0.001$). For finasteride, the hirsutism score went from 19.1 at baseline to 11.3 at 12 months, a 41% reduction ($p < 0.001$). Flutamide was more effective and had fewer side effects than finasteride in this study.

63. (2) **Iorizzo M** et al. Finasteride treatment of female pattern hair loss. Arch Dermatol 2006;142: 298–302.

Thirty-seven women with female-pattern hair loss were treated with oral finasteride, 2.5 mg/day, while taking an oral contraceptive containing drospirenone and ethinyl estradiol. Treatment efficacy was evaluated using global photography and the hair density score from videodermoscopy. A self-administered questionnaire was used to assess patient evaluation of treatment effectiveness. Sixty-two percent of the patients demonstrated some improvement of their hair loss with the use of finasteride, 2.5 mg/d, while taking the oral contraceptive. It is unclear whether the success was due to a higher dosage of finasteride (2.5 mg instead of 1 mg) or to its association with the oral contraceptive containing drospirenone, which has an antiandrogenic effect. Further studies are necessary to understand which patterns of female-pattern hair loss respond better to this treatment.

64. (4) **Palomba S** et al. Evidence-based and potential benefits of metformin in the polycystic ovary syndrome: A comprehensive review. Endocr Rev 2009;30:1–50

This review was aimed at describing all evidence-based and potential uses of MET in PCOS patients. In particular, the uses of MET were analyzed not only for the treatment of all PCOS-related disturbances such as menstrual disorders, anovulatory infertility, increased abortion, or complicated pregnancy risk, hyperandrogenism, endometrial, metabolic and cardiovascular abnormalities but also for the prevention of the syndrome

65. (4) **Lord JM** et al. Insulin-sensitising drugs (metformin, troglitazone, rosiglitazone, pioglitazone, D-chiroinositol) for polycystic ovary syndrome. Cochrane Database Syst Rev 2003;(2):CD003053. doi:10.1002/14651858.CD003053.

66. (2) **Harborne LR** et al. Metformin and weight loss in obese women with polycystic ovary syndrome: Comparison of doses. J Clin Endocrinol Metab 2005;90:4593–4598.

The aim of this study was to determine whether different doses of MET (1,500 or 2,550 mg/day) would have different effects on body weight, circulating hormones, markers of inflammation, and lipid profiles. The study included prospective cohorts randomized to two doses of MET. The patients studied were obese (BMI, 30–37 kg/m^2; n = 42) and morbidly obese (BMI, >37 kg/m^2; n = 41) women with PCOS. The main outcome measures were changes in body mass, circulating hormones, markers of inflammation, and lipid profiles. Intention to treat analyses showed significant weight loss in both dose groups. Only the obese subgroup showed a dose relationship (1.5 and 3.6 kg in 1,500- and 2,550-mg groups, respectively; $p = 0.04$). There were no differences in the other measured parameters.

67. (1) **Tang T** et al. Combined lifestyle modification and metformin in obese patients with polycystic ovary syndrome. A randomized, placebo-controlled, double-blind multicentre study. Hum Reprod 2006;21:80–89.

A randomized, placebo-controlled, double-blind study of obese (BMI > 30 kg/m^2), oligo-/amenorrhoeic women with PCOS. MET (850 mg) twice daily was compared with placebo over 6 months. All received the same advice from a dietitian. The primary outcome measures were (1) change in menstrual cycle, (2) change in anthropometric measurements, and (3) changes in the endocrine parameters, insulin sensitivity, and lipid profile. A total of 143 subjects were randomized (MET = 69; placebo [PL] = 74). Both groups showed significant improvements in menstrual frequency (median increase [MET = 1, $p < 0.001$; PL = 1, $p < 0.001$]) and weight loss (mean [kg] [MET = 2.84; $p < 0.001$ and PL = 1.46; $p = 0.011$]). However, there were no significant differences between the groups (95% CI, 1.001, 1.266). There were no significant changes in insulin sensitivity or lipid profiles in either of the groups. Those who received MET achieved a significant reduction in waist circumference and free androgen index. MET does not improve weight loss or menstrual frequency in obese patients with PCOS. Weight loss alone through lifestyle changes improves menstrual frequency.

68. (2) **Romualdi D** et al. Selective effects of pioglitazone on insulin and androgen abnormalities in normo- and hyperinsulinemic obese patients with polycystic ovary syndrome. Hum Reprod 2003;18:1210–1218.

Eighteen obese PCOS patients were treated with pioglitazone (45 mg/d) and evaluated for clinical signs, hormonal and lipid profile assays, and with oral glucose tolerance tests and euglycemic hyperinsulinemic clamps. Body weight, body fat distribution, and blood pressure remained stable throughout the treatment while hirsutism and acne significantly improved ($p < 0.001$). A restoration of menstrual cyclicity was observed at visit 4 in 83% ($p < 0.001$) of H-PCOS and in 33% of N-PCOS. A decrease in LH, LH/FSH ratio, androstenedione, and 17-hydroxy-progesterone was observed in both groups.

69. (1) **Baillargeon JP** et al. Effects of metformin and rosiglitazone, alone and in combination, in nonobese women with polycystic ovary syndrome and normal indices of insulin sensitivity. Fertil Steril 2004;82:893–902.

One hundred lean PCOS subjects were randomized to receive either MET, 850 mg; rosiglitazone, 4 mg; placebo; or both. Frequencies of ovulation were higher after treatment with an insulin-sensitizing drug (ovulations per subject in 6 months: MET, 3.3; rosiglitazone, 2.4; and combination, 3.4) than with placebo (0.4). Ovulatory frequencies increased significantly more with MET than with rosiglitazone, and the combination was not more potent. After treatment, serum free testosterone levels were comparable among all active treatment groups (MET, 2.34 pg/ml; rosiglitazone, 3.06 pg/ml; and combination, 2.39 pg/ml) and were significantly lower than in the placebo group (7.26 pg/ml). Compared with placebo, fasting insulin levels; area under the insulin curve during OGTT, the homeostatic model assessment of insulin sensitivity; and OGTT-derived ISI improved significantly after MET or combination therapies, but not after rosiglitazone alone.

70. (1) **Lemay A** et al. Rosiglitazone and ethinyl estradiol/cyproterone acetate as single and combined treatment of overweight women with polycystic ovary syndrome and insulin resistance. Hum Reprod 2006;21(1):121–128.

    Twenty-eight obese women with PCOS and elevated insulin levels not improved with diet were treated with either OCP containing ethinyl estradiol and the antiandrogen cyproterone acetate or the TZD rosiglitazone for 6 months. After this, both groups received a combination of both agents. In the first group, androgen levels and hirsutism were improved, but an increase in triglycerides and LDL cholesterol was found with no improvement in insulin sensitivity. In the second group, insulin sensitivity improved, with little effect on lipids, androgens, or hirsutism. In combination, improvement occurred in all parameters without a difference in side effects.

Precocious Puberty

71. (4) **Kaplowitz PB,** Oberfield SE. For the Lawson Wilkins Pediatric Endocrine Society: Reexamination of the age limit for defining when puberty is precocious in girls in the United States: Implications for evaluation and treatment. Pediatrics 1999;104:936–941.

    Recommendations based on the Pediatrics Research in Office Settings Network cross-sectional study of 17,077 girls between the ages 3 and 12 years. Breast development occurred earlier than in earlier studies at about age 9.96 years in whites and 8.87 in blacks. With 2.5 to 3 SDs below normal mean, white girls younger than age 7 and black girls younger than age 6 would be considered precocious.

72. (2) **Feuillan PP** et al. Long-term testolactone therapy for precocious puberty in girls with the McCune-Albright syndrome. J Clin Endocrinol Metab 1993;7:647–651.

    This was a prospective study of 12 girls at the National Institute of Child Health and Human Development using the aromatase inhibitor testolactone in the treatment of precocious puberty secondary to the McCune-Albright syndrome. The response to treatment was variable and had no impact on final predicated AH because of the development of CPP triggered by early exposure to sex hormones.

73. (3) **Roth C** et al. Effective aromatase inhibition by anastrozole in a patient with gonadotropin-independent precocious puberty in McCune-Albright syndrome. J Pediatr Endocrinol Metab 2002;15(suppl 3):945–948.

    A patient with McCune-Albright syndrome (café-au-lait spots; thelarche at age 2–6/12 years; menarche at 5–5/12 years; accelerated bone age [BA, 10 years]) was treated with the highly selective aromatase inhibitor anastrozole (1 mg/d). Estradiol levels were normal; anastrozole treatment and accelerated BA progressed only 6 months during 2.5 years of treatment. The potent estrogen-suppressive action and simple dosage regimen of anastrozole suggest it may be advantageous compared with other aromatase inhibitors such as testolactone or antiestrogens.

74. (2) **Laue L** et al. Treatment of familial male precocious puberty with spironolactone and testolactone. N Engl J Med 1989;320:496–502.

    This was a small study of nine boys between ages 3.3 and 7.0 with familial male precocious puberty. After the failure of single-agent therapy, spironolactone and testolactone were combined for a period of 6 to 12 months. This combination controlled symptoms of acne, erectile function, and aggression in all boys. Mean predicted height before and after therapy were not significantly different. With therapy, six of nine boys had development of CPP, which limited overall benefit.

75. (2) **Leschek EW** et al. Six-year results of spironolactone and testolactone treatment of familial male-limited precocious puberty with addition of deslorelin after central puberty onset. J Clin Endocrinol Metab 1999;84:175–178.

    Combined treatment with spironolactone, testolactone, and GnRHa (to help prevent central activation) was studied in 10 boys with familial male-limited precocious puberty. GnRHa was

added an average of 2.6 years after starting the earlier therapies. The growth rate normalized by 1 year and remained normal for the remaining 5-year treatment ($p < 0.001$).

76. (2) **Lenz AM** et al. Bicalutamide and third-generation aromatase inhibitors in testotoxicosis. Pediatrics 2010;126(3):e728–e733.

This study evaluated the response to therapy in two boys.

77. (2) **Reiter EO** et al. Bicalutamide plus anastrozole for the treatment of gonadotropin-independent precocious puberty in boys with testotoxicosis: A phase II, open-label pilot study (BATT). J Pediatr Endocrinol Metab 2010;23(10):999–1009.

Fourteen boys were treated in a single-arm, phase 2 pilot trail with bicalutamide (12.5, 25, 50, or 100 mg) and anastrozole at either 0.5 or 1 mg/d. At 1 year, mean (SD) change from baseline in growth rate was −1.6 (±5.1) cm/y and −0.1 (±1.8) SD units, and in bone maturation, −2.3 (±0.5) years. The bone age/chronologic age ratio was reduced from 2.1 (±0.6) at baseline to 1.0 (±0.4) ($p = 0.00013$). Gynecomastia (42.9%) and breast tenderness (12.5%) were the most common treatment-related adverse events.

78. (2) **Holland FJ** et al. Ketoconazole in the management of precocious puberty not responsive to LHRH-analogue therapy. N Engl J Med 1985;312:1023–1028.

This was a 1-year study of three boys aged 3.3 to 3.9 years old with precocious puberty unresponsive to GnRHa treated with ketoconazole. The testosterone level decreased by 2 days and normalized in two boys and reduced significantly in the third boy, with clinical improvement in behavior and growth velocity.

79. (4) **Partsch CJ** et al. Management and outcome of central precocious puberty. Clin Endocrinol 2002;56:129–148.

GnRH testing is needed for diagnosis of CPP. Earlier GnRHa trials demonstrate preserved height potential with treatment, although no randomized trials exist on FH in CPP. GnRHa therapy does not improve FH if given past age 8 years in girls.

80. (4) **Rosenfield RL.** Selection of children with precocious puberty for treatment with gonadotropin-releasing hormone analogs. J Pediatr 1994;124:989–991.

Review of the literature and recommendations for GnRH analogues in CPP based on the literature. Because few prospective data are available, these recommendations remain to be tested in long-term prospective studies.

81. (2) **Paterson WF** et al. Auxological outcome and time to menarche following long-acting goserelin therapy in girls with central precocious or early puberty. Clin Endocrinol (Oxf) 2004;61:626–634.

In a study of 46 girls treated with GnRH analogue, 11 had reached their FH of 159.7 cm (−0.63 SD) compared with the mean parental target height of 160.9 cm. Nine of the eleven girls (82%) attained FHs within or above their target range. This subset of girls gained a statistically insignificant excess of weight but returned to pretreatment BMI at their FHs.

82. (2) **Tanaka T** et al. Results of long-term follow-up after treatment of central precocious puberty with leuprorelin acetate: Evaluation of effectiveness of treatment and recovery of gonadal function: The TAP-144-SR Japanese Study Group on Central Precocious Puberty. J Clin Endocrinol Metab 2005;90:1371–1376.

The effect of leuprorelin treatment on AH and recovery of reproductive function was observed in 63 girls and 13 boys with CPP. Mean treatment durations were 3.8 ± 2.0 and 4.1 ± 2.5 years, and posttreatment follow-up durations were 3.5 ± 1.3 and 2.6 ± 1.1 years for girls and boys, respectively. AH was 154.5 ± 5.7 cm for girls, and 89.5% of girls reached AH within their target height range. For boys, AH was 163.2 ± 13.0 cm, and 90.9% reached target height range.

83. (1) **Magiakoue** et al. J Clin Endocrinol Metab 2010;95(1):109–117..

The efficacy and safety of GnRH analogue treatment in childhood and adolescence: a single-center, long-term follow-up study. Forty-seven girls with CPP (out of a cohort of ninety-two girls with other disorders) were treated with GnRHa to final AH. Body composition, bone density, ovarian volume, LH, FSH, hirsutism and menstrual cycles were evaluated. Treated girls with ICPP were found to have no increase in obesity, hirsutism, and abnormal menstrual cycles and had normal BMD.

84. (2) **Ko JH** et al. Changes in bone mineral density and body composition in children with central precocious puberty and early puberty before and after one year of treatment with GnRH agonist. Horm Res Paediatr 2011;75(3):174–179.

Bone density and fat mass were assessed by DEXA in 121 Korean girls with CPP treated with GnRH agonist over 1 year. Increase in obesity did not occur. Progression of bone mass acquisition was not impaired.

85. (4) **Walvoord EC, Pescovitz OH.** Combined use of growth hormone and gonadotropin-releasing hormone analogues in precocious puberty: Theoretic and practical considerations. Pediatrics 1999;104:1010–1014.

Review of earlier trials with GnRHa only reveal final AHs that are 1 to 7 cm below that of the predicted height, although measurements improved 3 to 8 cm over those in patients who were not treated. The studies using combinations of GH with GnRHa have been small and inconsistent but tend to indicate benefit.

86. (2) **Pasquino AM** et al. Adult height in girls with central precocious puberty treated with gonadotropin-releasing hormone analogues and growth hormone. J Clin Endocrinol Metab 1999;84:449–452.

This was a small prospective study of 10 girls with CPP treated with depot GnRHa plus GH compared with 10 girls with CPP treated with GnRHa alone. Final AH gain with GnRHa with GH group was 7.9 cm compared with 1.6 cm with GnRHa alone ($p = 0.001$).

87. (2) **Pasquino AM** et al. Combined treatment with gonadotropin-releasing hormone analog and growth hormone in central precocious puberty. J Clin Endocrinol Metab 1996;81:948–951.

Ten girls and four boys with idiopathic CPP with low predicted height were studied with GnRHa plus growth hormone and compared with findings in ten girls and four boys who received only GnRHa. After 3 years, the PAH was increased significantly at 13.6 cm in the girls receiving combined therapy. No significant height difference was found in the boys.

88. (2) **Pucarelli I** et al. Effects of combined gonadotropin-releasing hormone agonist and growth hormone therapy on adult height in precocious puberty: A further contribution. J Pediatr Endocrinol Metab 2003;16:1005–1010.

This study compared 18 girls with idiopathic CPP treated with a combination of GnRH analogue and growth hormone with 17 subjects who declined growth hormone therapy. Treatment lasted 2 to 4 years. The GnRH agonist–alone group did not achieve an increase of final AH above PAH calculated for girls with accelerated growth, whereas it was higher than that calculated for average girls. The group treated with combination therapy achieved a final AH significantly greater than predicted with either method. The second group gained an additional 6 cm of AH compared with the first. The study demonstrates safety but still with a limited number of subjects.

89. (2) **Heger S** et al. Long-term outcome after depot gonadotropin-releasing hormone agonist treatment of central precocious puberty: Final height, body proportions, body composition, bone mineral density, and reproductive function. J Clin Endocrinol Metab 1999;84:4583–4590.

This was a prospective multicenter trial of 50 women with CPP treated with depot GnRHa for a mean of 4.4 years with therapy ending at a mean age of 11.0 years. About 80% of the women reached a FH within the target height range, whereas before treatment, only 56% of the women had a PAH within the target range.

90. (1) **Proos LA** et al. Can the TW3 bone age determination method provide additional criteria for growth hormone treatment in adopted girls with early puberty? A comparison of the Tanner-Whitehouse 3 method with the Greulich-Pyle and the Tanner-Whitehouse 2 methods. Horm Res Paediatr 2010,73(1):35–40.

Forty-six adopted girls with early or precocious puberty were randomly assigned to treatment with either GnRHa or GnRHa combined with GH and followed to FH. It was found that FH was significantly higher in the combined treatment group, 158.9 cm compared with 155.8 cm in the GnRHa treated group. Using the Gruelich-Pyle method gave the most accurate prediction of FH on GnRHa therapy alone and therefore also yielded the best grounds for the selection of patients who might benefit the most from combination therapy. AH derived from the use of both GP and the Tanner-Whitehouse three methods of prediction AH was useful in prediction in patients treated with combination therapy with GnRHa and growth hormone.

Male Hypogonadism

91. (3) **Feldman HA** et al. Impotence and its medical and psychosocial correlates: Results of the Massachusetts Male Aging Study. J Urol 1994;151:54–61.

92. (2) **Bacon CG** et al. Sexual function in men older than 50 years of age: Results from the health professionals follow-up study. Ann Intern Med 2003;139:161–168.

A cross-sectional analysis of data collected by questionnaires from a prospective cohort of 3,174 men aged 53 to 90 years to describe the association between age and several aspects of sexual functioning in men older than 50 years of age. The age-standardized prevalence of erectile dysfunction in the previous 3 months was 33%. Many aspects of sexual function (including overall

function, desire, orgasm, and overall ability) decreased sharply by decade after 50 years of age. Physical activity was associated with lower risk for erectile dysfunction, and obesity was associated with a higher risk. Smoking, alcohol consumption, and television viewing time were also associated with increased prevalence of erectile dysfunction.

93. (3) **Shores MM** et al. Arch Intern Med 2006;166:1660–1665.

This study evaluated whether low testosterone levels are a risk factor for mortality in male veterans, using a clinical database to identify men older than 40 years with repeated testosterone levels obtained from October 1, 1994 to December 31, 1999, and without diagnosed prostate cancer. A low testosterone level was a total testosterone level of less than 250 ng/dl (<8.7 nmol/l) or a free testosterone level of less than 0.75 ng/dl (<0.03 nmol/l). The risk for all-cause mortality was estimated using Cox proportional hazards regression models, adjusting for demographic and clinical covariates over a follow-up of up to 8 years. Mortality in men with normal testosterone levels was 20.1% (95% CI, 16.2%–24.1%) versus 24.6% (95% CI, 19.2%–30.0%) in men with equivocal testosterone levels and 34.9% (95% CI, 28.5%–41.4%) in men with low testosterone levels.

94. (2) **Laughlin** et al. Low Serum Testosterone and Mortality in Older Men. J Clin Endocrinol Metab 2008;93:68–75.

This study examined the association of endogenous testosterone levels with mortality in older community-dwelling men. This was a prospective, population-based study of 794 men, aged 50 to 91 (median 73.6) years who had serum testosterone measurements at baseline (1984–1987) and were followed for mortality through July 2004. All-cause mortality by serum testosterone level was measured. During an average 11.8-year follow-up, men whose total testosterone levels were in the lowest quartile (<241 ng/dl) were 40% (hazards ratio [HR], 1.40; 95% CI, 1.14–1.71) more likely to die than those with higher levels, independent of age, adiposity, and lifestyle. Additional adjustment for health status markers, lipids, lipoproteins, blood pressure, glycemia, adipocytokines, and estradiol levels had minimal effect on results.

95. (3) **Wu FCW** et al. Identification of late-onset hypogonadism in middle-aged and elderly men. N Engl J Med 2010;363:123–135.

A random population sample of 3,369 men between the ages of 40 and 79 years at eight European centers was evaluated to identify late-onset hypogonadism on the basis of an association between symptoms and a low testosterone level. Using questionnaires, data were collected with regard to the subjects' general, sexual, physical, and psychological health. Levels of total testosterone were measured in morning blood samples by mass spectrometry, and free testosterone levels were calculated with the use of Vermeulen formula. Symptoms of poor morning erection, low sexual desire, erectile dysfunction, inability to perform vigorous activity, depression, and fatigue were significantly related to the testosterone level. However, only the three sexual symptoms had a syndromic association with decreased testosterone levels. Late-onset hypogonadism can be defined by the presence of at least three sexual symptoms associated with a total testosterone level of less than 11 nmol/l (3.2 ng/ml) and a free testosterone level of less than 220 pmol/l (64 pg/ml).

96. (4) **Jockenhovel F**. Testosterone therapy—what, when and to whom? Aging Male 2004;7:319–324.

This review article outlines the indications for therapy in men with primary or secondary hypogonadism as well as age-related androgen deficiency. Various testosterone preparations are reviewed.

97. (2) **Snyder PJ** et al. Effects of testosterone replacement in hypogonadal men. J Clin Endocrinol Metab 2000;85:2670–2677.

Prospective study of 14 hypogonadal men taking transdermal testosterone followed up for 3 years showed increased spine and hip BMD and improved energy level and sexual function. Knee-flexion strength was unchanged, fat-free mass decreased, and lipid levels did not change.

98. (1) **Seidman SN** et al. Testosterone replacement therapy for hypogonadal men with major depressive disorder: A randomized, placebo-controlled clinical trial. J Clin Psychiatry 2001;62:406–412.

Thirty-two men with hypogonadism and depression were randomized to placebo or testosterone and observed during a 6-week follow-up. No difference was found between placebo and testosterone groups in depression, although the testosterone-treated group had improved sexual function.

99. (1) **Rabkin JG** et al. A double-blind, placebo-controlled trial of testosterone therapy for HIV-positive men with hypogonadal symptoms. Arch Gen Psychiatry 2000;57:141–147.

This double-blind, placebo-controlled 3-month trial of testosterone therapy in 74 patients demonstrated significant improvements in muscle mass, libido, energy levels, and depression.

100. (1) **Finkelstein JW** et al. Estrogen or testosterone increases self-reported aggressive behaviors in hypogonadal adolescents. J Clin Endocrinol Metab 1997;82:2423–2438.

This randomized, double-blind, placebo-controlled, crossover study included 35 hypogonadal boys starting depotestosterone who demonstrated increased physical aggression.

101. (4) **Darby E, Anawalt BD**. Male hypogonadism: An update on diagnosis and treatment. Endocrinol 2005;4:593–309.

A review article outlining the differential diagnosis of male hypogonadism, appropriate laboratory studies, and therapeutic options.

102. (1) **Boloña** et al. Testosterone use in men with sexual dysfunction: A systematic review and meta-analysis of randomized placebo-controlled trials. Mayo Clin Proc 2007;82(1):20–28

103. (1) **Calof M**, et al. Adverse events associated with testosterone replacement in middle-aged and older men: A meta-analysis of randomized, placebo-controlled trials. J Gerontol 2005;60A:1451–1457.

104. (1) **Haddad R**, et al. Testosterone and cardiovascular risk in men: A systematic review and meta-analysis of randomized placebo-controlled trials. Mayo Clin Proc 2007;82(1):29–39.

105. (2) **Fernández-Balsells MM** et al. Clinical review 1: Adverse effects of testosterone therapy in adult men: A systematic review and meta-analysis. J Clin Endocrinol Metab 2010;95:2560–2575.

106. (1) **Basaria S**, et al. Adverse events associated with testosterone administration. N Engl J Med 2010;363:109–122.

In a randomized trial, men 65 years of age or older who had low serum testosterone levels and limitations in mobility were assigned to either placebo or testosterone gel to be applied daily for 6 months. The primary end point was improvement in leg-press strength, which was greater with testosterone therapy than with placebo. However, the trial was stopped early because of a greater number of cardiac adverse events in the testosterone group.

Infertility

107. (3) http://www.cdc.gov/nchs/data/series/sr_23/sr23_025.pdf.

108. (3) **Hull MG** et al. Population study of causes, treatment, and outcome of infertility. Br Med J 1985;291:1693–1697.

Specialist infertility practice was studied in a group of 708 couples within a population of residents of a single health district in England. At least one in six couples needed specialist help at some time in their lives because of an average infertility of 2.5 years, 71% of whom were trying for their first baby. Those seen at gynecology clinics comprised 10% of new and 22% of all patient visits. Failure of ovulation (amenorrhea or oligomenorrhea) occurred in 21% of cases and was successfully treated (2-year conception rates of 96% and 78%, respectively). Tubal damage (14%) had a poor outlook (19%) despite surgery. Endometriosis accounted for infertility in 6%, although seldom because of tubal damage, cervical mucus defects, or dysfunction in 3% and coital failure in up to 6%. Sperm defects or dysfunction were the most commonly defined cause of infertility (24%) and led to a poor chance of pregnancy (0%–27%) without donor insemination. Obstructive azoospermia or primary spermatogenic failure was uncommon (2%), and hormonal causes of male infertility were rare. Infertility was unexplained in 28%, and the chance of pregnancy (overall, 72%) was mainly determined by duration of infertility. IVF could benefit 80% of cases of tubal damage and 25% of unexplained infertility (i.e., 18% of all cases, representing up to 216 new cases each year per million of the total population).

109. (4) **Cooper TG** et al. World Health Organization reference values for human semen characteristics. Hum Reprod Update 2009:1–15.

110. (2) **Nielsen MS** et al. Comparison of several one-step home urinary luteinizing hormone detection test kits to OvuQuick. Fertil Steril 2001;76:384–387.

This prospective cohort study examined the accuracy and ease of use of one-step home urinary LH-detection kits in 81 cycles in women undergoing artificial insemination. Three different kits detected an LH surge within 12 hours, all with similar accuracy, making the detection of ovulation for fertility management easy and accurate.

111. (4) The Practice Committee of the American Society for Reproductive Medicine. Use of clomiphene citrate in women. Fertil Steril 2006;86(suppl 4):S187–S193.

112. (4) The Practice Committee of the American Society for Reproductive Medicine. Use of exogenous gonadotropins in anovulatory women: A technical bulletin. Fertil Steril 2008;90(suppl 3):S7.

113. (1) **Madgar I** et al. A controlled trial of high spermatic vein ligation for varicocele in infertile men. Fertil Steril 1995;63:120–124.

In this randomized, controlled study of high-ligation treatment of varicocele, a significant increase in pregnancy was seen in the first year after surgery compared with findings in a group that waited 1 year before having surgery, with 44.4% pregnancies in the first year compared with 10% in the nonoperated-on group. The group that waited also had a significant increase in pregnancies in the year after surgery, at 60% over a 1-year period.

114. (1) **Bouloux PG** et al. Induction of spermatogenesis by recombinant follicle-stimulating hormone (puregon) in hypogonadotropic azoospermic men who failed to respond to human chorionic gonadotropin. J Androl 2003;24:604–611.

A multicenter, open-label, randomized efficacy and safety study was performed with combined hCG and recombinant FSH (rec-FSH) (PuregonT) treatment to induce spermatogenesis in hypogonadotropic hypogonadal male patients. A weekly dose of 450 IU (3 × 150 IU or 2 × 225 IU) recFSH, in addition to hCG, was able to induce spermatogenesis in many hypogonadotropic azoospermic men who failed to respond to treatment with hCG alone.

115. (1) **Vandekerckhove P** et al. Clomiphene or tamoxifen for idiopathic oligo/asthenospermia (Cochrane Review). In: The Cochrane Library. 3rd ed. Oxford: Update Software, 2002.

Five prospective, randomized studies involving 738 men demonstrated a beneficial effect of antiestrogens on testosterone levels, but no difference in the pregnancy rate was found with an OR of 1.26 (95% CI, 0.99–1.56). The overall pregnancy rate was 15.4% in the treated groups compared with 12.5% in the control groups.

116. (1) **Ghanem H**. Combination clomiphene citrate and antioxidant therapy for idiopathic male infertility: A randomized controlled trial. Fertil Steril 2010;93:2232–2235.

Sixty infertile men with idiopathic oligoasthenospermia were randomized in a placebo-controlled trial to assess the combination of clomiphene citrate 25 mg/d and the antioxidant vitamin E 400 mg/d. The pregnancy OR was 3.76 (95% CI, 1.03–13.64) with a 36.7% pregnancy rate compared to 13.3% in the control group. There were significant improvements in semen parameters.

117. (2) **Cohlen BJ** et al. Timed intercourse versus intra-uterine insemination with or without ovarian hyperstimulation for subfertility in men (Cochrane Review). In: The Cochrane Library. 3rd ed. Oxford: Update Software, 2002.

Seventeen trials comprising 3,662 completed cycles were studied and demonstrated improved pregnancy rates with natural cycle IUI compared with timed intercourse. The OR was 2.43 (95% CI, 1.54–3.83). When combined with controlled ovarian hyperstimulation, IUI improved pregnancy rates compared with timed intercourse with an OR of 2.14 (95% CI, 1.30–3.51).

118. (2) **van Rumste MME** et al. Intra-cytoplasmic sperm injection versus partial zona dissection, subzonal insemination and conventional techniques for oocyte insemination during in vitro fertilization (Cochrane Review). In: The Cochrane Library. 3rd ed. Oxford: Update Software, 2002.

A review of 10 studies, 8 of which compared ICSI with conventional IVF. In men with normal semen on analysis, no difference in pregnancy rates occurred with ICSI compared with conventional IVF. With a borderline result on semen analysis, ICSI was significantly better than conventional IVF with an OR of 3.79 (95% CI, 2.97–4.85) for fertilization rate per oocyte, although no data on pregnancy rate were compiled.

119. (1) **Pandian Z** et al. In vitro fertilisation for unexplained subfertility (Cochrane Review). In: The Cochrane Library. 3rd ed. Oxford: Update Software, 2002.

Four randomized, controlled trials of IVF were studied in unexplained infertility. No difference was noted in pregnancy rates between IVF and IUI with and without hyperstimulation, with an OR of 0.51 (95% CI, 0.23–1.1) in nonstimulated IUI cycles and with an OR of 0.87 (95% CI, 0.42–1.8) in IUI cycles with ovarian stimulation.

120. (1) **Hughes E** et al. Clomiphene citrate for unexplained subfertility in women (Cochrane Review). In: The Cochrane Library. 3rd ed. Oxford: Update Software, 2002.

In six studies, clomiphene citrate demonstrated improved pregnancy rates compared with placebo, with an OR of 2.5 (95% CI, 1.35–4.62). It was noted that the risk of ovarian cancer may be increased in women who had 12 cycles of clomiphene or more, although it is not clear whether the infertility is the cause of this finding or whether the medication was responsible.

121. (2) **Hughes E** et al. Clomiphene citrate for ovulation induction in women with oligoamenorrhea (Cochrane Review). In: The Cochrane Library. 3rd ed. Oxford: Update Software, 2002.

Four crossover studies are reviewed. Clomiphene treatment increased pregnancy rate, with an OR of 3.41 (95% CI, 4.23–9.48).

122. (4) **Bristow RE, Karlan BY**. Ovulation induction, infertility, and ovarian cancer risk. Fertil Steril 1996;66:499–507.

This review of four earlier case-control studies, three retrospective cohort studies, and a meta-analysis of three case-control studies and three retrospective cohort studies, as well as a large meta-analysis of three additional case-control studies, indicates that infertility is an independent risk factor for ovarian cancer, and the increased risk is not likely related to fertility medications.

123. (1) **Guzick DS** et al. Efficacy of superovulation and intrauterine insemination in the treatment of infertility. N Engl J Med 1999;340:177–183.

This was a randomized controlled clinical trial of 932 couples with unexplained infertility comparing treatment with ICI, IUI, IUI with superovulation, and ICI with superovulation. IUI with superovulation produced a pregnancy rate of 33%, which was significantly increased over ICI and IUI alone, compared with 18% in the IUI-alone group, 19% in the superovulation with ICI group, and 10% with the ICI-alone study subjects. IUI-alone and ICI with superovulation outcomes were significantly improved over ICI alone.

124. (2) **Jain T** et al. Comparison of basal follicle-stimulating hormone versus the clomiphene citrate challenge test for ovarian reserve screening. Fertil Steril 2004;82: 180–185.

A meta-analysis, including 12 studies of basal FSH values, to evaluate the predictive value in pregnancy outcomes.

125. (3) **Klein J, Sauer MV**. Assessing fertility in women of advanced age. Am J Obstet Gynecol 2001;185:758–770.

If the basal FSH is normal, further assessment should be obtained by administering clomiphene, 100 mg, days 5 to 9, with a repeated FSH on day 10. If the pretreatment day 3 FSH or day 10 posttreatment FSH is elevated, then the patient has diminished ovarian reserve and is less likely to become pregnant.

126. (3) **de Vet A** et al. Anti-Müllerian hormone serum levels: A putative marker for ovarian aging. Fertil Steril 2002;77:357–362.

This longitudinal observational study followed 41 premenopausal and 13 postmenopausal women to assess concentrations of antimüllerian hormone, FSH, inhibin B, and estradiol and number of ovarian follicles by ultrasonography approximately 3 years apart. Serum antimüllerian hormone levels declined over time while other measurements did not. AMH may be the best marker for ovarian aging.

Menopause

127. (1) **MacLennan A** et al. Oral oestrogen replacement therapy versus placebo for hot flushes (Cochrane Review). In: The Cochrane Library. 3rd ed. Oxford: Update Software, 2002.

This is an analysis of 21 double-blind, randomized, placebo-controlled trials of oral HRT therapy involved a total of 2,511 women observed from 3 months to 3 years. HRT decreased hot flashes by 77% (95% CI, 58.2–87.5) compared with findings in placebo.

128. (1) **Notelovitz M, Mattox JH**. Suppression of vasomotor and vulvovaginal symptoms with continuous oral 17-beta-estradiol. Menopause 2000;7:310–317.

Oral 17β-estradiol was studied in a randomized, double-blind, multicenter, parallel-group study of 145 postmenopausal women. Hot flashes were significantly reduced by 83% ($p < 0.001$) in the estrogen-treated group. Vaginal dryness was reduced 86.1% with estrogen.

129. (1) **Eriksen B**. A randomized, open, parallel-group study on the preventive effect of an estradiol-releasing vaginal ring (Estring) on recurrent urinary tract infections in postmenopausal women. Am J Obstet Gynecol 1999;180:1072–1079.

This was a randomized prospective study of 53 women treated with a vaginal estrogen ring compared with 55 untreated women. Incidence of urinary tract infection was significantly higher in the untreated women ($p = 0.008$).

130. (1) **Cardozo L** et al. Meta-analysis of estrogen therapy in the management of urogenital atrophy in postmenopausal women: Second report of the Hormones and Urogenital Therapy Committee. Obstet Gynecol 1998;92:722–727.

This meta-analysis of nine randomized controlled studies demonstrated a significant benefit of estrogen, regardless of route of administration, on urogenital atrophy.

131. (1) **Brown JS** et al. Urinary tract infections in postmenopausal women: Effect of hormone therapy and risk factors. Obstet Gynecol 2001;98:1045–1052.

HERS was a randomized, blinded secondary prevention trial of HRT (conjugated equine estrogen/medroxyprogesterone acetate [CEE/MPA]) and heart disease in 2,763 postmenopausal women (aged 44–79 years). Urinary tract infection frequency was not improved in the HRT group, with an OR of 1.16 (95% CI, 0.99–1.37).

132. (1) **Soares CN** et al. Efficacy of estradiol for the treatment of depressive disorders in perimenopausal women: A double-blind, randomized, placebo-controlled trial. Arch Gen Psychiatry 2001;58:529–534.

This was a randomized, double-blind, placebo-controlled trial of estrogen in 50 postmenopausal women with depressive disorders. Depression significantly decreased in 68% of women treated with 17β-estradiol compared with 20% of placebo-treated patients ($p = 0.001$).

133. (1) **Zweifel JE, O'Brien WH**. A meta-analysis of the effect of HRT upon depressed mood. Psychoneuroendocrinology 1997;22:189–212.

This was a meta-analysis of 14 RCTs and 12 cohort studies of estrogen and depression in postmenopausal women, demonstrating significant improvement on estrogen.

134. (1) **Hlatky MA** et al.; for the Heart and Estrogen/Progestin Replacement Study (HERS) Research Group. Quality-of-life and depressive symptoms in postmenopausal women after receiving hormone therapy: Results from the Heart and Estrogen/Progestin Replacement Study (HERS) trial. JAMA 2002;287:591–597.

This was a randomized clinical trial of HRT therapy in older postmenopausal women with preexisting coronary heart disease. Most women did not have vasomotor symptoms and did not improve with HRT. In women with vasomotor symptoms, depression was improved by HRT.

135. (1) **Espeland MA** et al. Conjugated equine estrogens and global cognitive function in postmenopausal women: Women's Health Initiative Memory Study. JAMA 2004;23:2959–2968.

In this randomized double-blind placebo-controlled trial, 2,808 (ages 65–79) women enrolled in the WHI and "free of probable dementia" were assessed for global cognitive function with a Modified Mini-Mental State Examination (3MSE) yearly for a mean of 5.4 years. The 1,387 subjects receiving 0.625 mg of conjugated estrogen were compared with 1,421 placebo-treated matched controls. The estrogen-treated group had a lower score (and estrogen plus progesterone in another arm of the trial also yielded lower results; $p < 0.04$ for estrogen alone, and $p < 0.006$ for estrogen plus medroxyprogesterone acetate). The risk of having a 10-U decrease in the 3MSE score was 1.47 (CI, 1.04–2.07) for estrogen versus placebo. It was noted that having a lower cognition at baseline worsened the outlook, but removing women with stroke, dementia, and mild cognitive impairment from the analysis lessened the difference.

136. (4) **Maki PM**. A systematic review of clinical trials of hormone therapy on cognitive function: Effects of age at initiation and progestin use. Ann N Y Acad Sci 2005;1052:182–197.

This literature review suggested that a potential benefit of postmenopausal estrogen use may exist in selected cognitive domains, especially in newly menopausal and symptomatic women and little evidence for benefit at ages older than 65.

137. (2) **Grodstein** et al. A prospective, observational study of postmenopausal hormone therapy and primary prevention of cardiovascular disease. Ann Intern Med 2000;133(12):933–941.

In a prospective, observational cohort study 70,533 postmenopausal women were followed from 1976 to 1996, taking either conjugated estrogen 0.3 mg or 0.6 mg/d, compared to no therapy. One thousand two hundred fifty-eight major coronary events (nonfatal myocardial infarction or fatal coronary disease) and 767 strokes occurred. When all cardiovascular risk factors were considered, the risk for major coronary events was lower among current users of hormone therapy, including short-term users, compared with never-users (RR 0.61)

138. (2) **Grodstein F** et al. Postmenopausal hormone use and secondary prevention of coronary events in the Nurses' Health Study: A prospective, observational study. Ann Intern Med 2001;135:1–8. (LOE 2b)

In the Nurses Health study, 2,489 postmenopausal women with previous myocardial infarction or documented atherosclerosis were followed from 1976 to 1996. There were 213 cases of recurrent nonfatal myocardial infarction or coronary death. Events were lower in current users than in never-users (RR, 0.38 [CI, 0.22–0.66]). No clear differences emerged between users of estrogen alone and users of estrogen combined with progestin. Overall, with up to 20 years of follow-up, the RR for a second event among current users of hormone therapy was 0.65 (CI, 0.45–0.95) compared with never-users. The risk for recurrent major coronary events seems to increase among short-term hormone users with previous coronary disease but to decrease with longer-term use.

139. (1) **Grady D** et al. Cardiovascular disease outcomes during 6.8 years of hormone therapy: The heart and Estrogen/Progestin Replacement study follow-up the (HERS II) JAMA 2002;288(1):49–57.

Postmenopausal women with previously diagnosed CHD were randomized to CEE+/MPA or placebo and followed for an average of 4.1 years. The primary outcome was nonfatal myocardial infarction and CHD death. Secondary cardiovascular events included coronary revascularization, hospitalization for unstable angina or congestive heart failure, nonfatal ventricular arrhythmia, sudden death, stroke or transient ischemic attack, and peripheral arterial disease. Lower rates of CHD events among women in the hormone group in the final years of HERS did not persist during additional years of follow-up. After 6.8 years, hormone

therapy did not reduce risk of cardiovascular events in women with CHD. The overall HRs were similar after adjustment for potential confounders and differential use of *statins* between treatment groups

140. (1) **Manson** et al. Estrogen plus progestin and the risk of coronary heart disease. N Engl J Med 2003;349(6):523–534.

    Primary prevention trial included 16,608 postmenopausal women 50 to 79 years old at baseline, treated with CEE 0.625 mg + MPA 2.5 mg or placebo. The primary efficacy outcome was CHD, defined as either MI or CHD death. The study was terminated after mean follow-up of 5.2 years, instead of the planned 8.5 years because of an increased risk of breast cancer, with a HR of 1.26 for treated subjects. The HR for CHD was 1.24.

141. (1) **Rossouw J** et al. Postmenopausal Hormone Therapy and Risk of Cardiovascular Disease by Age and Years Since Menopause, JRossouw JAMA,2007, *297(13):1465–77*

    In a data reanalysis in 10,739 women in WHI (both estrogen alone and estrogen/progesterone therapy), cardiovascular events occurred in 396 treated women versus 379 placebo-treated women. Hazard ratio was above 1.0 only in women over 70 and over 20 years from the onset of menopause.

142. (1) **Hylley S** et al. Noncardiovascular disease outcomes during 6.8 years of hormone therapy (HERS II). JAMA 2002;288:58–66.

    The RR for venous thromboembolism in HERS II was 2.08 overall over a 6.8-year period (CI, 1.28–3.40). The RR for biliary surgery was 1.48 (CI, 1.12–1.95), but no difference was found in overall mortality rates.

143. (4) American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for the Diagnosis and Treatment of Menopause. AACE Menopause Guidelines Revision Task Force. Updated review of menopause and hormone replacement therapy guidelines.

144. (1) **Chlebowski RT** et al. Estrogen plus progestin and breast cancer incidence and mortality in postmenopausal women. JAMA 2010;304(15):1684–1692.

    Breast cancers in the estrogen-progestin group were similar in histology and grade to breast cancers in the placebo group but were more likely to be node positive (81 [23.7%] vs. 43 [16.2%], respectively; HR, 1.78; 95% CI, 1.23–2.58). However, deaths directly attributed to breast cancer (25 deaths [0.03% per year] vs. 12 deaths [0.01% per year]; HR, 1.96; 95% CI, 1.00–4.04), did not meet statistical significance, since the CI included 1.

145. (1) **Anderson** et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: The Women's Health Initiative randomized controlled trial. JAMA 2004;291(14):1701–1712.

    Conjugated estrogen (0.625 mg) was compared to placebo in a RCT involving 10,739 postmenopausal women aged 5 to 79 years old who had a prior hysterectomy. The study was begun in 1993 and was terminated at 6.8 years because global adverse events, primarily CVA and VTE exceeded predetermined safety thresholds. In this study, the primary outcome of cardiovascular events showed a HR of 0.91 in treated versus control subjects, while the HR for breast cancer was only 0.77 in treated versus control subjects.

146. (2) **Fournier** et al. Unequal risks for breast cancer associated with different hormone replacement therapies: Results from the E3N cohort Study. Breast Cancer Res Treat 2008;107:103–111.

    The French E3N prospective cohort study reports on a 12-year follow-up of 80,377 women age 40 to 65 comparing HRT never-users to ever-users. Those using estrogen-progesterone or estrogen dydrogesterone showed no significant increased risk of any breast cancer subtype. However, estrogen combined with various other progestagens was associated with significant increases in risk of ductal and lobular carcinomas (1.69) (CI, 1.50–1.91).

6

Diabetes Mellitus

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TYPE 1 DIABETES MELLITUS

Definition

Type 1 diabetes mellitus (DM) is a chronic metabolic disorder of glucose homeostasis that manifests secondary to absolute lack of insulin.

Etiology

It is thought that, in humans, environmental factors such as diet, severe stress, and possibly viral infections, among other unknown factors, may trigger a T cell–mediated autoimmune destruction of pancreatic beta cells in a susceptible host, which leads to onset of type 1 DM. Family studies failed to identify a specific mendelian pattern of inheritance for this disease [1,2]. However, multiple genetic loci are strongly linked to the development of this polygenic disorder, especially human leukocyte antigen (HLA)-DR and HLA-DQ alleles of the histocompatibility complex. Having a specific genotype that is associated with type 1 DM does not necessarily result in development of this disease; in more than half of monozygotic twins of patients with diabetes, type 1 DM will not develop, which suggests an important role for environmental factors in the etiology of this disease. Furthermore, most patients (85%) lack a family history of a similar disorder.

Genetics

Major Histocompatibility Complex Genes

Major histocompatibility complex (MHC) class II molecules attach to exogenous peptides and then present these peptides on the cell surface for T-cell (CD4) recognition. In humans, class II loci (HLA-DR, HLA-DP, HLA-DQ) of the MHC class II are located on chromosome 6. The finding that type 1 DM develops in 30% to 50% of monozygotic twins, whereas it occurs in only 15% of HLA-identical sibs, indicates that although MHC genes are strongly associated with increased risk for type 1 DM, other genes must be involved in the etiology of this disease. MHC class I alleles are also associated with type 1 DM although with a lesser effect.

Insulin-Dependent Diabetes Mellitus Genes

Multiple other genes are suspected in the development of type 1 DM. These genes are termed insulin-dependent DM (IDDM) genes. IDDM1 is the HLA region locus mentioned previously. IDDM 2 is a nonhistocompatibility gene located on chromosome 11, which contains the insulin gene. Changes in the promoter region of the insulin gene increase the risk of type 1 DM. In addition, other genes have been associated with type 1 DM; these include protein tyrosine phosphatase, nonreceptor type 22 (PTPN22) gene on chromosome 1, interleukin-2 receptor alpha gene (IL2RA), cytotoxic T-lymphocyte antigen 4 (IDDM 12, which lies on chromosome 2), interferon induced with helicase c domain 1 (IFIH1), vitamin D receptor (VDR), and others [3].

Rare Forms

Type 1 DM is rarely caused by single gene mutation; examples include the immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX), and the autoimmune polyendocrine syndrome type 1.

Epidemiology

Based on National American Health Service surveys, the prevalence of diabetes among people younger than 20 years is around 2 per 1,000 in the United States. Worldwide incidence and prevalence rates vary significantly, depending on the population, ethnicity, and geography, which suggest an important role for environmental factors. In the United States, the overall incidence of type 1 DM is around 20 per 100,000 per year (Rochester, MN, data 1970–1979). Incidence of type 1 DM is two to three times more common in whites than in other ethnic groups in the United States. Interestingly, incidence rates of type 1 DM are increasing worldwide.

Type 1 DM also develops in adults; the incidence is estimated around 8.2 per 100,000 annually [4].

Pathophysiology

The development of type 1 DM starts with an unknown precipitating event in a genetically susceptible host (stage 1) that triggers a T cell–mediated autoimmune destruction of beta cells (stage 2). Over time, generally months to years, progressive loss of insulin is noted and can be detected by using intravenous glucose tolerance tests (stage 3). Subsequently, blood glucose starts to increase, indicating significant beta cell damage (stage 4); this stage may last for several months in children or a longer period in adults and is characterized by clinical diabetes in the presence of normal or low C-peptide levels. Finally, in stage 5, insulin and C-peptide production ceases, and the subject becomes dependent on exogenous insulin for survival.

Diagnosis

Screening

Diabetes develops in 2% to 5% of relatives of patients with type 1 DM. Numerous antibodies directed against islet cell antigens have been identified, but few are of value as research screening tools [5]. In the research setting, autoantibodies are commonly used to predict type 1 DM in studies involving relatives of patients with diabetes [6]. Using low titers as diagnostic values predicts future development of type 1 diabetes in a highly sensitive manner, but this, of course, is associated with a significant number of false-positive results. Therefore, researchers use combination autoantibodies with the intravenous glucose tolerance test to increase the specificity and yield of these tests.

Serum Antibodies

The presence of serum islet cell cytoplasmic antibodies (ICAs) is a highly predictive marker for future development of type 1 DM in relatives of family members with that disease. The sensitivity is higher than 80%, and the specificity is higher than

90%. However, these values change significantly depending on the cutoff titers used. The exact antigenic molecules responsible for ICAs are not fully identified [7]. The sensitivity of Glutamic Acid Decarboxylase (GAD) antibodies and ICA 512 is between 65% and 70% and is highly specific (typically >90%). GAD is expressed in the islets of Langerhans and also in neurons and gonadal tissue.

Insulin autoantibodies (IAAs) are less sensitive markers than ICAs (25% sensitivity); however, IAAs correlate well with the short duration to development of disease as well as young-age onset of disease. Antibodies against zinc transporter antigen 8 (ZnT8) were detected in previously classified type 1 negative autoantibody status. Risk for diabetes increases with higher titers of ICA and the presence of multiple autoantibodies. Autoantibodies may be of value to screen the high-risk population, but lack of an effective intervention is the main barrier against recommendation of such a practice.

First-Phase Insulin Release

Measuring first-phase insulin release during an intravenous glucose tolerance test increases the predicted value of screening with autoantibodies [8]. First-phase insulin release is consistent with progress of diabetes from stage 2 to stage 3. A finding of insulin release that is below the first percentile confers a 90% risk of type 1 diabetes in 3 years in patients with positive ICAs and positive IAAs.

Monogenic Forms of Diabetes Syndromes

Sometimes the diagnosis of type 1 diabetes from other rare diabetes syndromes is not clear from autoantibody studies. Recent advances in commercially available genetic testing allow the distinction of type 1 diabetes from the rather rare monogenic forms of diabetes that include maturity-onset diabetes of the young (MODY) and neonatal diabetes. Genetic screening for monogenic diabetes should be considered in the following clinical scenarios: diabetes diagnosed within 6 months of birth and in children diagnosed with diabetes without autoantibodies (indicative of type 1) or signs of insulin resistance (obesity, acanthosis nigricans indicative of type 2 diabetes).

Clinical Manifestations

The most common presenting symptoms are polydipsia and polyuria. Other symptoms frequently encountered in children and adolescents are fatigue, weight loss, and abdominal pain, as well as enuresis. Diabetic ketoacidosis (DKA) is a presenting symptom in 10% to 40% of cases. Frequency of this presentation varies significantly between different countries and may depend on public education, incidence of diabetes in that region, and presence of other people with diabetes in the family, resulting in early detection before development of DKA. These symptoms are not specific for type 1 diabetes and can occur in patients with type 2 diabetes, including DKA.

Most patients with type 1 diabetes are diagnosed at a young age (typically, less than 30 years); furthermore, in recent years, an increasing number of adolescents have been diagnosed with type 2 DM, especially those who are obese.

Laboratory Findings

The laboratory glucose values used for diagnosis type 1 DM are fasting plasma glucose of 126 mg/dl (7 mmol/l) on more than two occasions or 2-hour glucose value of 200 mg/dl (11.1 mmol/l) or higher during oral glucose tolerance testing. Recently in 2010, glycosylated hemoglobin A_{1c} (A1C) of greater than or equal to 6.5% has been accepted by American Diabetes Association (Clinical Practice Recommendations 2010) as diagnostic for diabetes.

Prevention

Prevention of type 1 DM is still in early research stages [9,10]. Currently, no effective preventive strategies exist. Immunomodulating drugs (e.g., azathioprine

and cyclosporine) and nicotinamide prevented further beta cell destruction in small studies for a short time. The short-term benefits were not sufficient to indicate long-term use of these potentially toxic medications. The Diabetes Prevention Trial (DPT-1) demonstrated that using injectable or oral insulin does not prevent diabetes in relatives of patients with diabetes. Ongoing studies are evaluating the effect of oral insulin on subpopulations of relatives of patients with diabetes.

Treatment

Insulin

Only insulin is used to control blood glucose in type 1 diabetes. Animal-derived insulins have long been passed over in favor of genetically engineered so-called human insulins. The goal of treatment is to achieve near-normal plasma glucose around the clock. Intensive therapy delays the onset and progression of microvascular complications of diabetes but may not affect macrovascular mortality [11,12]. The main disadvantages of intensive therapy are the increased frequency of hypoglycemia, ketoacidosis, and weight gain [13]. Ideally, reducing the hemoglobin A1c to less than 7% (ADA) is the goal in type 1 DM patients [14]. Patients are typically educated about recognizing and treating hypoglycemia at the same time they learn about using insulin.

Insulin Regimens

Conventional Therapy. The regimen of twice-daily injections with basal insulin (typically intermediate-acting insulin) and a bolus insulin (regular or rapid-acting analogues)—known as conventional therapy—is associated with variable and inferior glycemic control in comparison with intensive insulin therapy regimens and therefore has been abandoned in favor of other insulin regimens. Evidence supports intensive glycemic control by using multiple daily injections or insulin pump rather than two-injection conventional therapy [15]. A twice-daily split insulin regimen (conventional therapy) and once-daily injections are not recommended because of difficulty in achieving the goal and the inability to adjust insulin doses appropriately to prevent hyperglycemia in type 1 DM. These two modalities of treatment, however, are frequently used by general practitioners at the onset of disease until the patient is transferred to the care of a specialist.

Intensive Insulin Therapy. Insulin pump: Portable, external insulin infusion pumps have undergone significant improvement in the past two decades [16]. Insulin is delivered continuously at a set basal rate (~60% of total daily insulin). Pumps can be programmed to increase the basal insulin at night to counteract morning hyperglycemia. At mealtime, bolus doses of insulin are provided to cover meal glucose excursions. Use of such a pump requires frequent monitoring of blood glucose and predisposes to site infections and DKA but usually results in better glycemic control.

Multiple Daily Injections: Multiple daily injections (MDIs) refer to three or more injections with very-rapid-acting analogues before meals. In addition, basal insulin is provided at dinner (glargine or detemir) or at bedtime (NPH or glargine or detemir) for background coverage over a 24-hour period. Frequently, if NPH or detemir is used, a second dose is provided before breakfast. In type 1 DM, intensive insulin therapy (pumps or MDIs) provides lower hemoglobin A_{1c} and significantly reduces the risk of microvascular complications. These data are derived primarily from the results of the Diabetes Control and Complications Trial (DCCT/EDIC) cohort, which also involved a comprehensive patient support program of diet, exercise, and close supervision with instructions.

Table 6.1. Insulin Types and Timeframe of Action

Insulin	Onset (hr)	Peak (hr)	Duration (hr)
Regular	0.5	2–4	6–8
Aspart, glulisine, lispro	0.2	1–2	3–4
NPH	2	6–10	12–18
Glargine	2	Peakless	Up to 24
Detemir	2	Peakless	Up to 24

Types of Insulin

- *Very-rapid-acting insulin analogues*. The available agents, insulin aspart (NovoLog), insulin glulisine (Apidra), or insulin lispro (Humalog), are engineered so that after injection, the insulin dissociates quickly from the aggregate. Therefore, these insulins have rapid onset of action and short duration of activity (Table 6.1). These agents are used specifically to lower glucose after a meal and to correct postprandial hyperglycemia and therefore are called "meal" insulins. These insulins are at least as effective as regular insulin [15,17–19]. Furthermore, their use can reduce the frequency of hypoglycemia and can be safely used in patients with unpredictable eating patterns.
- *Regular insulin*. The main disadvantage for use of regular insulin is the need to inject it 30 to 45 minutes before meals, which may be inconvenient or may be associated with hypoglycemia if the meal is delayed or not eaten.
- *Intermediate-acting insulin*. Neutral protamine Hagedorn (NPH) insulin has a longer duration of action than regular insulin and is used mainly to provide basal insulin coverage [20]. NPH insulin does not work fast enough to control postprandial glucose level right after administration but may be used to over a meal 4 to 5 hours after injection. When administered at bedtime, NPH is as effective in reducing fasting plasma glucose as long-acting insulin analogs, but increases the risk of nocturnal hypoglycemia [3].
- *Long-acting insulin analogues*. Glargine (Lantus) and detemir (Levemir) are long-acting synthetic preparations that are relatively peakless, with a lower incidence of hypoglycemia and a prolonged duration of action. The main disadvantage is that they cannot be mixed with other insulins. Detemir insulin, although has a shorter half-life than glargine, produces similar effects to glargine when administered properly.
- *Premixed insulins*. Mixtures of two kinds of insulin do not allow for flexibility and require more skill in adjustment of insulin to achieve a therapeutic end, and thus, such a combination should not be the drug of choice.
- Jet injectors have been used with success by patients or caregivers that are unable to use a standard syringe/needle technique.

Pramlintide

- *Pramlintide*: Pramlintide (15–60 μg) is a synthetic analogue of human amylin that slows gastric emptying and lowers A_{1c} concentrations mainly by reducing postprandial glucose excursions. In patients with type 1 diabetes, it is used only with meal time insulins. It is recommended to reduce the insulin dose by 50% when pramlintide is started.

- *Inhaled insulin:* The first commercially available inhaled insulin (Exubera) was pulled from the market due to poor acceptance by patients and health professionals. One formulation of very-rapid-acting inhaled insulin is still undergoing clinical development and whether this is approved by the Food and Drug Administration and becomes commercially available has yet to be determined.

Diet

- Dietary management regimens improve glycemic control, but insufficient evidence is available to recommend a specific diet plan over another. Dietary knowledge is essential for carbohydrate counting if used in patients using MDIs or insulin pumps. Eating disorders are more common in type 1 DM, especially in adolescents, and this adversely influences glycemic control. Therefore, regular psychological assessment and instruction regarding healthy eating habits are recommended [22].

Exercise

Aerobic exercise is recommended. In addition, persistent training with light weights and high repetitions could be useful [23]. Of note, exercise during a state of insulin deficiency as manifested by higher blood glucose before the activity may be associated with hyperglycemia subsequent to exercise, and therefore, blood glucose monitoring is helpful, especially in cases of unanticipated exercise [24]. Insulin should not be injected into the exercising limb because continuous muscle movement results in increased insulin release. The abdomen is the preferred site for insulin injection.

High-intensity exercise may result in increased albuminuria and may in theory be associated with adverse effects. However, no evidence supports clinical progression of retinopathy or kidney disease with high-intensity exercise. The risk of myocardial infarction (MI) is higher in people with type 1 DM, and thus, the American Diabetes Association recommends cardiac stress exercise testing for patients who are older than 35 years, who have been diagnosed with type 1 diabetes for longer than 15 years (especially those who have evidence of clinical autonomic neuropathy, peripheral vascular disease, or microvascular disease), or who have a significant cardiovascular risk profile. The evidence to support such recommendations is inadequate.

Blood Glucose Monitoring

Learning blood glucose self-monitoring skills is essential for type 1 DM. It is important for patients with diabetes to monitor for hypoglycemia and significant hyperglycemia to avoid complications. Little evidence indicates that frequent blood glucose self-monitoring translates to better glucose control by using standard glucometers. This might be secondary to lack of adjustment or intervention by physicians or patients. The use of laser blood glucose monitoring devices, home glycated hemoglobin monitors, fructosamine monitors, and measurement of advanced glycation end products by skin autofluorescence has not been shown to provide advantage over standard methods. Blood glucose monitors with electronic voice and integrated lancing-blood sample monitors are effective and helpful in blind patients. Continuous-monitoring real-time glucose sensors are helpful in adjusting insulin doses and are used typically over a period of 72 hours to obtain data. Glucose measurements using these devices correlate very well with standard glucometer readings. Such devices in patients with type 1 or type 2 DM were superior to standard meters in reducing duration of hyperglycemia and hypoglycemia and are used for prolonged time (more than 72 hours) in patients with type 1 DM and hypoglycemia unawareness that require glucagon or serious resuscitation.

Transplantation

Pancreas transplantation is considered in patients planning to have a kidney transplant for treatment of end-stage renal disease, given that pancreas transplantation may improve the survival of the transplanted kidney, may improve hypoglycemia, and may partially reverse neuropathy. Pancreas transplantation alone may be considered in patients with severe complications of diabetes. Islet cell transplantation has a significant advantage over whole-pancreas transplantation but requires special experience that is not available in many centers. In addition, a sufficient supply of islet cells is lacking. Stem cell transplantation has been attempted in small numbers of patients with type 1 DM.

Diet

Dietary management regimens improve glycemic control, but insufficient evidence is available to recommend a specific diet plan over another. Dietary knowledge is essential for carbohydrate counting if used in patients using MDIs or insulin pumps. Eating disorders are more common in type 1 DM, especially in adolescents, and this adversely influences glycemic control. Therefore, regular psychological assessment and instruction regarding healthy eating habits are recommended [22].

TYPE 2 DIABETES MELLITUS

Definition

Type 2 DM is a chronic disorder of glucose homeostasis characterized by hyperglycemia and impaired insulin action, with abnormal pancreatic insulin secretion as well as increased rates of hepatic glucose production. Unlike type 1 DM, no absolute physiologic lack of insulin is present; rather, a state of relative insulin deficiency develops.

Etiology

The concordance rate of type 2 DM in identical twins is 70% to 90%, with a strong familial clustering of type 2 DM, suggesting a genetic etiology. No specific gene has been identified as the cause of type 2 DM, and multiple genetic abnormalities may be involved. Insulin resistance alone does not explain diabetes; impaired beta cell function manifested as impaired first- and second-phase insulin secretion combined with a decline in incretin action is also implicated. It is clear that type 2 diabetes has both environmental (associated with obesity, nutrition, and/or reduced activity) and genetic components.

Risk Factors

1. Overweight and Obesity. Risk for type 2 DM increases with obesity as measured by the body mass index (BMI) in both men and women [25]. Overweight is considered BMI greater than or equal to 25 kg/m^2. Central fat (so-called apple distribution) increases the risk of type 2 DM in addition to BMI measurements. Central obesity is defined as a waist circumference greater than 40 inches in men and greater than 35 inches in women. Weight gain in adulthood of more than 10 kg in men or more than 8 kg in women is associated with increased risks of DM regardless of the BMI.
2. Ethnicity. The reasons behind ethnic variation are unclear, but general themes were observed among minorities at increased risk for diabetes (e.g. Pima indians and micronesian Nauru). These include abandoning traditional lifestyle behaviors and adopting new behaviors that include reduced physical activity and increased caloric intake.
3. Family history of type 2 DM, especially in first degree relatives

4. Patients with elevated fasting glucose measurements (100–125 mg/dl) or with high postprandial measurements (2 hr OGTT value 140–199 mg/dl) and/or A1C 5.7% to 6.4%.
5. Lack of exercise or physical inactivity. This is an independent risk factor from the BMI.
6. Dyslipidemia (HDL < 35 mg/dl and/or triglycerides >250 mg/dl)
7. Hypertension (>140/90 mmHg) or treated for high blood pressure
8. History of gestational diabetes mellitus (GDM) or baby weight greater than 9 lbs (4 kg)
9. Syndromes associated with insulin resistance (severe obesity, polycystic ovary syndrome and/or acanthosis nigricans)

Epidemiology

Based on US national health surveys from the Centers for Disease Control and Prevention, it is estimated that approximately 26.4 million in the United States have diabetes that equals approximately 8.3% of the population. The prevalence of diabetes increases with age, and 20% of subjects older than 65 have diabetes. Worldwide, the prevalence of diabetes differs significantly between one region and another, with some areas having extremely high prevalence (e.g., Micronesian Anurans rates ~40%).

Diabetes is the sixth leading cause of death in the United States, and most deaths are attributed to heart disease. The American Diabetes Association estimates health care costs that are specifically due to diabetes (direct medical costs) at $116 billion in 2007, plus another $58 billion in indirect costs of disability, work loss, and premature mortality.

Pathophysiology of Type 2 Diabetes Mellitus

Three primary pathophysiologic features of type 2 DM are insulin resistance, relative insulin deficiency, and impaired incretin action. Insulin resistance in muscle, liver, and adipose tissue is related to weight gain. Through complex perturbations in insulin signaling pathways and fuel metabolism (beyond the scope of this chapter), these tissues become resistant to insulin. Early on in the progress from normal glycemia to prediabetes and eventually type 2 DM, the pancreas responds by secreting excessive insulin to overcome the insulin resistance. With time, the pancreas cannot keep up with the demand, and a state of relative insulin deficiency occurs marked by elevation in both fasting BG, due to improper suppression of hepatic gluconeogenesis, and postmeal hyperglycemia. Many factors lead to the decline in insulin secretion including a loss of first-phase insulin secretion and a blunted second phase. Gut hormones like glucagon-like peptide-1 and glucose-dependent insulinotropic peptide improve insulin secretion and beta cell function/health, and as diabetes develops, there level or action in the body declines partially, causing the decline in beta cell function. Other factors may include severe glucotoxicity and lipotoxicity that may impede normal beta cell function. An important feature of type 2 DM is that the disease is progressive in nature, and insulin resistance tends to remain high throughout the disease, and beta cell function continues to decline.

Diagnosis

Clinical Manifestations

Unlike patients with type 1 DM, most patients with type 2 diabetes do not show the classic symptoms of hyperglycemia, as mentioned previously. Recent estimates by the Centers for Disease Control and Prevention (CDC) estimate 7 million patients in the United States are undiagnosed with DM. The most common classic symptoms in type 2 DM are excessive thirst followed by easy fatigability, neurologic symptoms, blurred vision, and/or recurrent infections.

Laboratory Findings

Plasma glucose levels that are thought to be, in the long term, associated with retinopathy and proteinuria are used to diagnose diabetes. Several diagnostic modalities have been proposed to separate those patients with hyperglycemia who are at increased risk for development of microvascular complications from those who are at low risk but who do have hyperglycemia. Currently, two main diagnostic criteria are used: the American Diabetes Association criteria, which use fasting plasma glucose, and the World Health Organization criteria, which depend on oral glucose tolerance test results. Various populations were followed up prospectively by using a 2-hour glucose test after a 75-g glucose load for the development of microvascular complications. A postchallenge plasma glucose level of 200 mg/dl (11.1 mmol/l) seemed to differentiate reliably subjects who experience microvascular complications from those who do not. These studies are the basis of the World Health Organization diagnostic system.

In 2010, the American Diabetes Association added glycosylated hemoglobin (A1c) greater than or equal to 6.5% to its list of diagnostic criteria for type 1 and type 2 DM. With the standardization of the A1C assay, it has become a widely accepted means to diagnosis diabetes. The ADA retains the other three diagnostic criteria of a fasting plasma glucose level of greater than or equal to 126 mg/dl (7 mmol/l), random plasma glucose greater than or equal to 200 mg/dl (11.1 mmol/l) plus symptoms, and 75-g oral glucose tolerance test 2-hour value of greater than or equal to 200 mg/dl (11.1 mmol/l) as acceptable diagnostic criteria for DM. All diagnostic tests should be confirmed on a subsequent day unless signs of unequivocal hyperglycemia.

Screening

Identifying patients with asymptomatic diabetes is an effective strategy because of the availability of effective treatments that reduce the morbidity and the progression of disease. The American Diabetes Association recommends screening overweight adults 45 years or older every 3 years as the consensus. Opportunistic screening patients younger than 45 years old with multiple risk factors is also encouraged because the incidence and prevalence of type 2 DM are increasing in children, adolescents, and young adults. Risk factors (described in detail above) include family history of diabetes, overweight defined as BMI of 25 kg/m^2 or higher, habitual physical inactivity, being a member of a high-risk ethnic or racial group, previously identified impaired fasting glucose or impaired glucose tolerance, hypertension, dyslipidemia, history of gestational DM or delivery of a baby weighing more than 9 lb (4 kg), polycystic ovary syndrome, and/or acanthosis nigricans.

Prevention

The most effective recommendation to prevent diabetes is to engage in lifestyle modifications that lower caloric intake and increase physical activity, ultimately resulting in modest weight loss (5%–7% body weight). Metformin is increasingly being used off-label to prevent diabetes. Data from the Diabetes Prevention Study (DPP) revealed that metformin was most effective in people with BMI greater than 35 kg/m^2 and was ineffective at preventing diabetes in lean patients. Note that lifestyle intervention is effective at all BMIs to prevent diabetes and has shown to be an effective prevention strategy for all people at risk of diabetes. Angiotensin converting enzyme inhibitors (ACE inhibitors) and angiotensin receptor blockers (ARBs) have been associated with diabetes prevention as secondary end points; however, in prospective trial, they have not shown to be effective at preventing diabetes [10].

Treatment

Weight Reduction and Dietary Restrictions

The effect of diet on glucose control is observed early, before any demonstrable weight loss. Weight loss itself is also associated with significant improvement in glycemic control, whether it is through diet and exercise, behavioral modification, weight loss medications, or bariatric surgery [27]. Programs that are associated with 5% to 10% weight loss in 3 to 4 months result in significantly improved glycemic control. Larger weight loss percentage may result in normalization of fasting glucose in newly diagnosed patients with diabetes. In the UK Prospective Diabetes Study (UKPDS), patients with mild fasting hyperglycemia were more likely to normalize glucose measurements than were patients with higher fasting glucose measurements [28]. Using a very-low-calorie diet (800 kcal/d) produces greater initial improvement in glycemic control than low-calorie diets (1,000–1,200 kcal/d), but no measurable difference exists between these diets in the long term at 6 to 12 months. Using Orlistat (120 mg t.i.d.) in patients with type 2 DM is associated with modest weight loss but also with a reduced need for insulin or oral diabetes medicines and improved A_{1c} (0.5% over placebo).

Exercise

Exercise in combination with diet results in maintenance of weight loss and therefore is recommended for patients with type 2 DM [29]. Research has shown that a modest weight reduction of 5% to 7% of body weight and an increase in physical activity to 150 minutes per week improves glucose control and prevents or delays the onset of diabetes [11].

Oral Drug Therapy (Table 6.2)

Biguanides

Metformin (500–2,550 mg/d) is available in immediate-release and also extended-release forms. In the UKPDS, overweight patients assigned to metformin had fewer diabetes-related complications and lower mortality rates than did those using insulin [30]. Compared with the conventionally treated group (using diet), patients using metformin had a 32% risk reduction for diabetes complications, a 42% risk reduction for diabetes-related death, and a 36% reduction for all-cause mortality. Therefore, metformin is recommended as the first-line oral agent to be used in patients with type 2 DM [31]. Metformin reduces plasma glucose mainly by altering hepatic gluconeogenesis and thereby reducing hepatic glucose release. Furthermore, insulin-stimulated glucose uptake in the muscle is also enhanced by the use of metformin. Metformin does not increase insulin release, and therefore, it is not associated with hypoglycemia and does not cause weight gain. Typically, metformin reduces hemoglobin A1c by 1 to 2 percentage points. The most common side effects are gastrointestinal (diarrhea and indigestion), but lactic acidosis, a very rare side effect, is the most serious adverse event and could be fatal, especially if metformin is used in patients with renal impairment, cardiac or pulmonary failure, or sepsis. The estimated glomerular filtration rate (eGFR) cutoff to safely use metformin has not been clearly delineated; however, recent evidence has shown that metformin can be used safely in stage 3 chronic kidney disease (CKD) yet remains absolutely contraindicated in CKD stages 4 and 5 (eGFR <30 ml/min).

Sulfonylureas

Second-generation sulfonylureas are used mainly in the United States and have replaced the first-generation agents tolbutamide and chlorpropamide. All agents,

Table 6.2. Common Oral Diabetes Therapies

Class	Examples	Action	A1C Lowering	Effect on Weight	Cost	Precautions/ Contraindications	Comments
Biguanide	Metformin	Inhibits gluconeogenesis	1.5%–2%	Neutral	$	Risk of lactic acidosis if renal impairment, severe liver disease, alcohol abuse, iodinated contrast agents	First-line therapy, no hypoglycemia, lactic acidosis is rare
Sulfonylurea	Glipizide, glyburide, glimepiride	Insulin secretagogue	1%–1.5%	Modest gain	$	Hypoglycemia; severe liver and renal disease	Many years experience, more effective early in disease
Meglitindes	Repaglinide	Insulin secretagogue	1%–1.5%	Modest gain	$$	Hypoglycemia	Take before meals; alternative to SU if severe hypoglycemia; can use with renal impairment
D-Phenyl-alanine derivative	Nateglinide	Insulin secreta-gogue	Up to 1%	Modest gain	$$	Lower dose if liver disease	Take before meals, alternative to SU if severe hypoglycemia; can use with renal impairment
Thiazolidin-edione	Pioglitazone, rosigli-tazone	Insulin sensitizer	1%–2%	Gain	$$$	CHF (NYHA Class 3 or 4), rosiglitazone may increase CV risk	Fluid retention, bone effects, no hypoglycemia; can use with renal impairment; pioglitazone recommended
Dipeptidyl peptidase 4 inhibitor	Sitagliptin, saxagliptin, linagliptin	Increases incretin levels (GLP-1 and GIP)	Up to 1%	Neutral	$$$	Use lower dose with renal impairment, history of pancreatitis	Well tolerated; no hypoglycemia; targets postmeal glucose
Alpha glu-cosidase inhibitor	Acarbose, miglitol	Slow breakdown of carbohydrate	~0.5%	Neutral	$$	Inflammatory bowel disease or other chronic intestinal dis-ease; severe renal impairment	Flatulence, abdominal pain and diarrhea com-mon; lowers postmeal BG

Key for approximate cost: $ = <$50/mo; $$ = $51–150/mo; $$$ = $151–250/mo.

however, reduce glucose levels effectively and are comparable in efficacy (lowering hemoglobin A_{1c} by 1%–2%). All sulfonylureas function by stimulating insulin release. Patients who fail to respond to sulfonylureas are typically thin and have low insulin levels [32]. The most common side effects are weight gain of 2 to 3 kg and hypoglycemia (1%–2%), especially in the elderly. The results of the UKPDS show that the use of sulfonylureas does not increase cardiovascular events or cardiovascular motility in comparison with findings in patients who are treated with diet alone [33]. Sulfonylureas are used in combination therapy with other oral agents, as well as insulin, with variable successful results [34–38].

Meglitinides

Repaglinide (0.5–16 mg/d) and nateglinide (60–360 mg/d) stimulate insulin release through a mechanism slightly different from that of sulfonylureas [41]. These medications have a short duration of action and therefore should be used before meals. While normally taken three times per day, meglitinides may be added for an extra meal (up to four doses per day) and should be not taken for skipped meals, reducing the risk of hypoglycemia. Meglitinides effectively reduce hemoglobin A_{1c} by up to 1.5%. Side effects include hypoglycemia and weight gain and should not be used in combination with sulfonylureas.

Thiazolidinediones

Rosiglitazone (2–8 mg/d) and pioglitazone (15–45 mg/d) mediate their effect by binding to nuclear receptor peroxisome proliferator-activated receptor-γ and enhance tissue (muscle) sensitivity to insulin. The most common side effects are weight gain and fluid retention (edema), so these medications should be avoided in patients with congestive heart failure, especially NYHA class III and IV. The original thiazolidinedione medication, troglitazone, was withdrawn from the market because of fatal hepatic disease. In clinical trials, rosiglitazone and pioglitazone did not show evidence of hepatotoxicity. These agents are effective as monotherapeutic agents or in combination therapy and reduce A1C by 1.0 to 1.5 percentage points. They can be used in patients with renal impairment and when used with insulin leads to increased risk of fluid retention.

The thiazolidinedione class has come under intense scrutiny in terms of safety. From the cardiovascular standpoint, pioglitazone appears to be the safer alternative as shown by no increased risk of CV events that was observed in the "PROactive" study. A meta-analysis published on major studies with rosiglitazone demonstrated a significant increased risk of CV events and trend toward increased mortality resulting in a black box warning [42]. More recently, rosiglitazone was placed in a risk evaluation and mitigation strategy (REMS) program by the FDA that requires written verification by physician that pioglitazone and other glucose-lowering therapies are not effective in lowering glucose in the patient and the potential for increased risk of CV events has been discussed with the patient. The use of pioglitazone, however, is being evaluated for possible association with increased bladder cancer. FDA 2010 safety announcement indicates an ongoing review for a possible increased risk.

Dipeptidyl-Peptidase 4 Inhibitors

The dipeptidyl-peptidase 4 (DPP-4) inhibitors sitagliptin (25–100 mg/d), saxagliptin (2.5–5 mg/d), and linagliptin (5 mg/d) work by inhibiting the enzyme responsible for the breakdown of the incretins glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP). The inhibition DPP-4 allows a two- to threefold increase in these incretins, resulting in increased insulin secretion and suppression of postmeal hyperglucagonemia. The DPP-4 inhibitors are very well tolerated and do not result in weight gain or increased risk of hypoglycemia

over placebo. When used as monotherapy or when added to other oral agents, DPP-4 inhibitors lower A1C up to 1 percentage point. A purported risk of pancreatitis with sitagliptin has not been substantiated in analysis of large commercial insurance databases [43]. Recently, the labeling for sitagliptin has been modified to require checking serum creatinine with corresponding creatinine clearance before initiating therapy and periodically thereafter to make sure patients with impaired kidney function are treated with the appropriate dose. No dose adjustments are required for linagliptin for patients with impaired renal and/or liver function

α-Glucosidase Inhibitors

Acarbose (75–300 mg/d) and miglitol (75–300 mg/d) inhibit α-glucosidase activity in the luminal intestinal brush border, leading to delay in absorption of carbohydrates and therefore producing a reduction in postprandial glucose concentrations [39,40]. These agents are frequently associated with bloating, flatulence, and diarrhea and therefore are not commonly prescribed. Typically, A1C decreases of ~0.5 percentage points without significant weight gain or hypoglycemia.

Bromocriptine

Bromocriptine, a medication used to treat hyperprolactinemia and galactorrhea for many years, has been approved for the treatment of type 2 diabetes [19]. Bromocriptine is a dopamine D (2) receptor agonist that has been shown to lower insulin resistance through a not completely understood mechanism (possibly through improving circadian rhythm). A rapid-release formulation (bromocriptine QR) has been developed that is taken in the morning and results in a modest reduction of A1C of up to 0.5 percentage points with no increased risk of hypoglycemia over placebo. Common side effects of bromocriptine QR are transient nausea and diarrhea. While not commonly used, where this class of medications fits in the scheme of type 2 diabetes is still evolving.

Colesevelam

Colesevelam (3.8–4.4 g/d), a bile-acid sequestrant used to treat primary hypercholesterolemia, is also approved to treat type 2 DM. While the glucose-lowering mechanism of action is not clearly delineated, it may work by inhibiting glucose production by the liver (gluconeogenesis) and may also stimulate incretin release. Addition of colesevelam to commonly used oral agents such as metformin or sulfonylurea results in an approximately 0.5 percentage point reduction in A1C in addition to modest low-density lipoprotein (LDL) lowering. The most common side effects are constipation and dyspepsia.

Noninsulin Injectable Therapies (Table 6.3)

Exenatide

Exenatide is GLP-1 mimetic (5–10 μg b.i.d.), discovered from the salivary secretions of the venomous Gila monster that is a GLP-1 receptor agonist. The initial dose of 5 μg exenatide is injected subcutaneously within 1 hour of the morning and evening meals and is titrated to 10 μg b.i.d. after 1 month based on the level of glycemic control and tolerability. Exenatide causes an increase in glucose-dependent insulin secretion and suppression of postmeal glucagon secretion that flattens postmeal glucose excursions, resulting in approximately 1 percentage point reduction in A1C [44]. Transient gastrointestinal side effects are very common. Most patients lose weight (3–5 kg typical response) with exenatide due to enhanced satiety, and there is no increased risk of hypoglycemia. Exenatide results in modest improvement in lipids and blood pressure that accompanies weight loss. Exenatide is usually used in combination with one or two oral diabetes therapies and was recently approved by the FDA for use with long-acting insulin (glargine).

Table 6.3. Injectable Noninsulin Diabetes Therapies

Class	Examples	Action	A1C Lowering	Effect on Weight	Cost	Precautions/ Contraindications	Comments
GLP-1 mimetic	Exenatide	GLP-1 receptor agonist	~1%	Modest weight loss	$$$$	Renal impairment (CrCl < 30), severe GI disease; pancreatitis (rare)	Transient GI side effects, BID dosing within 1 hr of meal; targets postmeal BG; no hypoglycemia
GLP-1 analog	Liraglutide	GLP-1 receptor agonist	1%–1.5%	Modest weight loss	$$$$	Contraindicated if history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2; pancreatitis (rare)	Transient GI side effects, once daily dosing; targets postmeal and fasting BG; no hypoglycemia

Key for approximate cost: $ = <$50/mo; $$ = $51–150/mo; $$$ = $151–250/mo; $$$$ = >$250/mo.

Liraglutide

Liraglutide is a GLP-1 receptor agonist (1.2–1.8 mg/d) that was designed to have a longer half-life of approximately 13 hours after subcutaneous injection. The addition of a 16-carbon palmitic fatty acid to GLP-1 creates an analog that binds with albumin in the bloodstream, protecting it from degradation by DPP-4 enzyme. Because of the longer half-life compared to exenatide, it can be injected one time per day at a consistent time before or after meals. When compared head-to-head with exenatide, it provides similar modest weight reduction (~3 kg) and slightly better A1C lowering [45]. This might be due to the improved fasting BG reduction found with the longer-acting GLP-1 receptor agonist. Like other GLP-1 agonists, transient gastrointestinal side effects are common. Liraglutide does not increase risk of hypoglycemia over placebo when used in monotherapy or other non–hypoglycemia-induced therapies such as metformin or thiazolidinediones. The medication has been found to cause C-cell tumors or MTC in rats so should not be used in patients with medullary thyroid carcinoma or MEN 2. Off-label use of liraglutide as a weight loss medication has been studied yielding modest weight loss in patients with prediabetes and those that are obese with normal glycemia [25].

Insulin

See the section on type 1 DM regarding types of insulins. Insulin therapy should not be delayed in patients with type 2 DM, especially if glycemic control is suboptimal with the use of noninsulin agents. The primary adverse effects are weight gain (4 kg) and hypoglycemia. No significant evidence indicates that exogenous insulin use is associated with cardiovascular events. In the UKPDS, the use of insulin or sulfonylureas was not associated with increased cardiovascular disease, in comparison with findings in patients treated with diet alone.

Once-Daily Injection Regimen: Either intermediate- or long-acting insulin is used in this regimen. This regimen is associated with fewer hypoglycemic episodes but usually results in variable suboptimal glucose levels.

Twice-Daily Injection: Prebreakfast and predinner twice-daily NPH (so-called split regimen) is used in type 2 DM patients especially outside the United States. If prelunch or bedtime glucose is elevated, then very-rapid-acting insulin is added (i.e., split mixed regimen), with effective results. In some patients, this regimen can be substituted with premixed insulin, but this has the disadvantage of not allowing proper adjustments of insulin doses.

Intensive Insulin Therapy: Similar to type 1 DM, the MDI regimen is sometimes used in type 2 DM, especially if patients seek a flexible regimen, but is associated with weight gain.

Pramlintide

See section on type 1 DM. Pramlintide (60–120 μg) has been used in type 2 DM patients in combination with insulin, sulfonylureas, and metformin.

Combination Therapy

Several combination regimens of sulfonylureas, metformin, or thiazolidinediones with insulin have been investigated and are successful in reducing A1C as well as fasting plasma glucose measurements, but these combinations are more expensive than insulin alone. Data from the UKPDS demonstrate that combination therapy is need in the majority of patients to achieve glycemic target of A1C less than 7%. Combination therapy also is often needed to maintain glycemic control with long-standing type 2 diabetes due to the progressive nature of the disease. Assuming that metformin should be considered first-line therapy for type 2 diabetes, considerations for selecting medication to add to metformin include:

1. Does self-monitoring BG data inform whether the fasting and/or postmeal BG remains elevated? If fasting blood glucose remains elevated, then the addition

of background insulin or pioglitazone should be considered. If postmeal BG remains elevated, then incretin-based therapies or insulin secretagogues should be considered.
2. Weight: Does the patient seek weight loss or at least weight maintenance? Incretin-based therapies are weight neutral or result in modest weight loss. Insulin and secretagogues cause weight gain.
3. What is the level of patient and provider fear of hypoglycemia? Incretin-based therapies and pioglitazone do not cause hypoglycemia above placebo, and insulin and insulin secretagogues increase risk of hypoglycemia.
4. What is the financial status of the patient and can they afford a branded medication? Metformin, Sulfonylureas and NPH insulin provide lower cost options than branded incretin-based therapies and pioglitazone.

Transplantation

Pancreatic transplantation is not recommended for patients with type 2 DM.

DIABETIC KETOACIDOSIS

Definition

DKA is an acute, life-threatening complication of diabetes characterized by hyperglycemia, ketonemia, and a wide anion-gap metabolic acidosis. DKA occurs mainly in patients with type 1 DM and may occur in other types of diabetes [46].

Etiology

Its etiology is absolute or relative insulin deficiency in the presence of excessive counterregulatory hormones, leading to numerous metabolic abnormalities, diuresis, and ketoacid accumulation. The process could be triggered by various precipitating factors (e.g., pneumonia, urinary tract infections, and other infections; 25%) [47] or stress associated with severe or acute illness, including coronary disease, gastrointestinal hemorrhage, and trauma (10%–20%). It can also be the first presentation of diabetes in a previously undiagnosed patient (10%–30%). In insulin-requiring patients with diabetes, omission of insulin or nonadherence to therapy or suboptimal dosing preoperatively or postoperatively may precipitate DKA (30%). In patients using insulin pumps, DKA occurs because of catheters that are dislodged or obstructed [13]. Finally, medications, especially those that increase insulin resistance (e.g., glucocorticoids, β-agonists, and sympathomimetics), can precipitate DKA.

Epidemiology

The incidence of DKA seems to be increasing. In the United States, the incidence of hospital admission increased from 4 per 1,000 to 12 per 1,000 from 1980 to 1989. Generally speaking, DKA occurs in patients with type 1 DM, but patients at high risk for DKA include those at extremes of age, those with poor prior glycemic control, and those who use insulin pumps [48,49]. The overall morality rates are about 2%, it is higher for non hospitalized patients.

Pathophysiology

Elevated levels of counterregulatory hormones are necessary for the development of DKA in patients with diabetes. Glycogenolysis is enhanced especially by glucagon, catecholamines, and low insulin levels. Furthermore, glucagon excess and insulin deficiency result in enzymatic changes in the liver that ultimately shift pyruvate away from glycolysis toward the glucose synthesis. Excessive counterregulatory hormones in the absence of insulin lead to lipolysis and excess free fatty acid release from adipose tissue, which is then converted to ketoacids in the liver. Ketoacids are buffered by bicarbonate, leading to its depletion.

Diagnosis

Laboratory Findings

No specific laboratory criteria exist for the diagnosis of DKA; however, the presence of wide anion gap [(Na + K) − (Cl + HCO_3) >16 mEq/l] and ketonemia in a patient with diabetes is consistent with DKA. Most patients' glucose levels are high, exceeding 250 mg/dl (14 mmol/l), but occasionally glucose levels are normal, especially if the episode is preceded by long periods of fasting. Hematocrit and mean corpuscular volume increase in DKA. Glucose enters the red blood cell easily despite lack of insulin, which leads to osmotic swelling of the blood cell. Serum sodium levels vary significantly despite total body sodium deficit. Triglyceride levels are frequently elevated, mainly as a result of insulin deficiency and reduced clearance, but they typically return to normal with proper treatment of DKA. Initially, serum potassium levels are high or high normal secondary to the dehydration of acidosis, although total body potassium stores are depleted. Serum phosphate levels are also elevated initially, and both potassium and phosphate decrease quickly and significantly with treatment of DKA. Both amylase and lipase levels may be elevated in DKA without abdominal symptoms of pancreatitis or even hypertriglyceridemia; however, careful evaluation for possible pancreatitis should be pursued if lipase is elevated.

Clinical Manifestations

Symptoms develop rapidly in patients using pumps but may take several days in other patients with diabetes. Ketonemia results in nausea and vomiting and the characteristic odor of acetone on the breath. Less frequently, abdominal pain is the presenting symptom. Hyperglycemia and diuresis produce symptoms of dehydration and may progress to hypovolemic shock. Metabolic acidosis causes rapid and deep respirations (Kussmaul sign). Impaired mentation is also seen in 10% of DKA patients and may quickly proceed to coma, especially if the serum osmolality exceeds 340 mOsm/kg.

Treatment

Fluid Replacement

Some controversy exists on how best to administer fluids in patients with DKA. In patients without renal impairment or shock, low-rate saline infusions of 500 ml/hr over 4 hours and then 250 ml/hr were more effective than more rapid rates of infusion. However, in the setting of hypotension, saline should be given more rapidly, and treatment should be guided by using central venous pressure measurements. Generally speaking, rates of 500 to 1,000 ml/hr of normal saline for the first 1 to 2 hours have been used to expand circulatory volume, followed by 250 to 500 ml/hr of normal saline or half-normal saline. It is generally accepted that half the estimated fluid deficit should be corrected in the first 12 hours. Dextrose and water should be added after glucose levels decrease to 250 mg/dl (14 mmol/l).

Insulin

With equivalent doses, intravenous insulin was shown to be as effective as subcutaneous or intramuscular insulin in reducing length of hospital stay, but intravenous insulin led to a faster initial decline in glucose and had more predictable effects [50]. Intravenous insulin should be administered early to reduce hospital stay and to ensure faster recovery. Low-dose insulin (e.g., 0.1 U/kg) is as effective as high-dose bolus therapy of 50 to 150 U and is associated with reduced instances of hypoglycemia and hypokalemia [51]. Therefore, the recommendation is for low-dose insulin bolus intravenously followed by maintenance therapy.

Maintenance Insulin

Intravenous insulin at a rate of 0.1 to 0.2 U/kg/hr is maintained until acidosis is mostly corrected (pH > 7.3, bicarbonate >18 mEq/l, or anion gap <14 mEq/l). Frequently, serum glucose decreases to less than 250 mg/dl (14 mmol/l) before acidosis is corrected. Insulin infusion should continue; however, a dextrose-and-water infusion should be started to prevent hypoglycemia. This practice of maintaining intravenous insulin is mainly to allow ketone clearance and correction of acidosis [52].

Bicarbonate

Controversy remains about the use of intravenous bicarbonate in DKA. No clear benefits were shown with intravenous bicarbonate administration with patients with pH that exceeds 6.9 [53,54], and it can be associated with adverse events of hypokalemia and cerebral edema in children [55]. Therefore, bicarbonate use is not recommended. No studies have addressed the use of bicarbonate in patients with severe acidosis (pH < 6.9) or hypotension. In these patients, the practice has been to administer bicarbonate in doses of 44 to 133 mEq. No evidence supports or opposes such a practice.

Potassium

Potassium levels decrease quickly with management of acidosis because of intracellular compartment shift. Therefore, if serum potassium levels are low or normal, intravenous potassium should be administered immediately. If potassium levels are elevated (>5.5 mEq/l), potassium administration could be delayed until levels decrease to less than 5.5 mEq/l and the patient can urinate. Potassium is administered in 20 to 40 mEq/l of fluid provided as potassium chloride.

Phosphate

Serum phosphate levels also decreased to normal levels with proper management of DKA. Potential risk is associated with moderate to severe hypophosphatemia, including rhabdomyolysis, hemolysis, and impaired cardiac function. However, these are rarely found clinically. In small studies, adding phosphate to intravenous fluid did not affect the rate of recovery and was associated with minimal and nonsignificant lower serum calcium levels [56]. Therefore, phosphate treatment is not recommended unless evidence is found of significant hypophosphatemia.

Finally, in treating DKA, special attention should be directed to identifying as well as treating the triggering factors (e.g., urine culture, chest radiograph, and electrocardiogram).

Monitoring Therapy

Most patients with DKA experience hyperchloremic acidosis with therapy, especially in the first 8 hours. Therefore, observing serum bicarbonate levels, anion gap, and pH is better than measuring any single parameter. Correction of two of the three parameters (bicarbonate >18, pH > 7.3, and anion gap <14 mEq/l) is considered an adequate target of therapy. Assessing levels of urinary ketones as measured by standard assays measures only acetone and acetoacetate but not the primary ketone formed in DKA, which is β-hydroxybutyrate, and therefore, management of urine ketones should not be a target of therapy. As DKA is treated, β-hydroxybutyrate is converted to acetoacetate as well as acetone, both of which are readily measured by urinalysis, and therefore, excessive urine ketones can be seen, whereas serum levels of β-hydroxybutyrate have attained normal levels.

Prognosis

Mortality rates vary between 0.5% and 3.3%. Most patients at increased risk of death with DKA are elderly patients who have shock, altered mentation, acute respiratory distress syndrome, high osmolality, severe hyperglycemia, and acidemia.

In children, cerebral edema carries a high risk of death or permanent damage [57–59]. In adults, clinically detectable cerebral edema is rare and usually asymptomatic, but minor elevation in cerebrospinal fluid pressures has been documented; however, it is usually transient.

HYPEROSMOLAR COMA

Definition

Hyperosmolar coma is defined as extreme hyperglycemia that is associated with hyperosmolality, dehydration, and altered mental status without overt ketosis.

Etiology

A serious infection or an acute illness usually precipitates hyperosmolar coma in patients with diabetes. For many patients, hyperosmolar coma is the first manifestation of type 2 diabetes and may be related to severe dehydration and lack of access to drinking water [60]. Noncompliance with insulin treatment and surgical trauma are other important precipitating factors [61].

Pathophysiology

Reduced insulin sensitivity or relative insulin deficiency leads to hyperglycemia (discussed earlier in this chapter). Hyperglycemia causes osmotic diuresis and results in significant dehydration. Overt ketosis does not form because insulin is not lacking, and low levels of insulin prevent lipolysis.

Epidemiology

Hyperosmolar coma is an uncommon but potentially fatal complication of diabetes [62,63]. Some 4,500 hospitalizations in the United States resulted from hyperosmolar coma in 1990, most in women older than 60 years. Mortality rates are high, ranging from 15% to 60%. Mortality correlates with high osmolality, azotemia, and age [64].

Diagnosis

Clinical Manifestations

Polydipsia, polyuria, weakness, and fatigue are present in most patients and may precede hospitalization by weeks. These symptoms are usually followed by progressive mental status impairment in 50% of patients. Seizures are not common, but symptoms may be similar to those of an acute stroke, and patients may be in a coma, especially if serum osmolality is very high. Fever, nausea, and vomiting are frequently present at diagnosis (40%–65%).

Laboratory Findings

Plasma glucose concentrations are usually significantly elevated—around 600 mg/dl (33 mmol/l) or higher. Serum osmolality is increased and usually more than 320 mOsm/l. Urea and sometimes creatinine are elevated because of dehydration. Minimal acidosis secondary to starvation and lactic acid accumulation as well as mild ketosis (i.e., starvation) may be present, but arterial pH is usually higher than 7.3.

Treatment

Treatment recommendations are derived from retrospective reports [65–68]. Very few studies have addressed treatment of hyperosmolar coma in diabetes [65]. Recommendations are derived from consensus statements and modified from treatment recommendations for ketoacidosis.

Fluids

The most essential part of such treatment is fluid management, preferably in the intensive care unit, with monitoring and under the guidance of central venous

pressure measurements. Normal saline is infused at a rate of 1,000 ml/hr for 1 to 2 hours to normalize blood pressure. In cases of severe dehydration, hypernatremia usually is present, and therefore, subsequent fluid infusions are managed with 0.45% saline or at rates of 250 to 500 ml/hr, or dextrose infusions can be used [65], especially if the glucose concentration decreases to 250 mg/dl (14 mmol/l) or lower. Typically, half the total body water deficit is corrected over a 12-hour period, and the remaining half is corrected over the next 1 or 2 days.

Insulin

Although evidence exists of insulin resistance in hyperosmolar conditions, high insulin doses are best avoided to reduce chances of hypoglycemia [52,67,68]. Insulin bolus of 0.05 to 0.1 U/kg followed by infusion of 0.1 U/kg/hr intravenously is frequently used. Insulin should be followed with dextrose-and-water fluid supplementation when plasma glucose is less than 250 mg/dl (14 mmol/l).

Electrolytes

In hyperosmolar coma, a state of total body potassium deficit is found. Serum potassium could decrease further with insulin treatment and dilution secondary to the effect of fluids. Potassium supplements should be provided as discussed in previous section.

Phosphate also is depleted, and monitoring phosphate levels is recommended. Providing phosphate in patients without moderate to severe hypophosphatemia remains controversial. Corrected serum sodium provides a better measure of sodium levels than does uncorrected sodium. Finally, tests to confirm an underlying etiology should be carried out (e.g., chest radiograph, urine and blood cultures, electrocardiogram, and others, as deemed necessary). After the episode has been treated and the etiology has been investigated, the patient is discharged, preferably while receiving insulin therapy.

HYPOGLYCEMIA

Definition

Hypoglycemia is defined as a plasma glucose level of 50 mg/dl (2.8 mmol/l) or less [69].

Classification

The term *asymptomatic hypoglycemia* describes the condition of patients whose laboratory glucose levels are low but who are not experiencing any symptoms. Mild hypoglycemia describes the condition in patients who experience adrenergic symptoms and respond quickly to an oral carbohydrate load. In moderate hypoglycemia, patients experience both adrenergic and neuroglycopenic symptoms but manage to treat themselves and initiate therapy. Severe hypoglycemia is a term limited to patients who need assistance to treat hypoglycemia and are unable to administer treatment by themselves. Severe hypoglycemia is a major factor preventing tight glucose control and is costly.

Etiology

This section focuses on the most common cause of hypoglycemia, which is exogenous insulin– or oral hypoglycemic agent–mediated hypoglycemia. Evidence supports the principle that glycemic goals and not the insulin regimen used determine the frequency of hypoglycemia [13]. Insulin treatment with rapid-acting agents is associated with a lower risk of hypoglycemia than is regular insulin [69], and the use of glargine and detemir insulin has been shown to be associated with less hypoglycemia than NPH insulin. Incidence of severe hypoglycemia is the same for animal-derived insulins and so-called human-engineered insulin

treatments [70,71]. Most episodes of hypoglycemia are related to lifestyle factors, especially missing meals [72,73]. Other predictors of severe hypoglycemia are previous episodes of severe hypoglycemia [74], hemoglobin A_{1c} levels less than 7% [75], hypoglycemia unawareness [76], autonomic neuropathy [77], and long duration of diabetes.

Pathophysiology

When plasma glucose levels approach the hypoglycemic range, predictable physiologic changes occur. Pancreatic insulin release is suppressed at plasma glucose levels of 75 to 85 mg/dl (4.2–4.7 mmol/l). When glucose levels decrease to less than 70 mg/dl (3.9 mmol/l), counterregulatory hormone (e.g., glucagon, epinephrine, and cortisol) and growth hormone secretion is enhanced, thus producing adrenergic symptoms. Finally, neuroglycopenic symptoms (impaired mental status) occur when glucose levels decrease to less than 45 to 50 mg/dl (2.5–2.8 mmol/l). These threshold numbers may vary with repeated recurrent hypoglycemia. For example, in patients with insulinoma or type 1 DM and frequent hypoglycemic episodes, the threshold for counterregulatory hormone release, and therefore, the initial hyperadrenergic symptoms are possible with less-elevated findings. Hypoglycemia unawareness occurs when the threshold of adrenergic symptoms becomes lower than that of neuroglycopenic symptoms so that patients may have impaired mental status as the first sign of hypoglycemia.

Epidemiology

Type 1 Diabetes Mellitus

In the DCCT [36,78,79], 65% of patients randomly assigned to the study's intensive insulin arm and 35% to the conventional arm experienced at least one episode of hypoglycemia that was considered severe over a period of 6.5 years. Most episodes of severe hypoglycemia occur at night, and adolescents are more prone than adults.

Type 2 Diabetes Mellitus

In the UKPDS during a 10-year period, 23% of patients treated with insulin experienced at least one episode of severe hypoglycemia compared with 4% treated with chlorpropamide and 6% with glibenclamide [36]. The difference between oral agents was not statistically significant. None of the patients using metformin experienced a major hypoglycemic episode in the UKPDS. Long-acting sulfonylureas (e.g., chlorpropamide and glibenclamide) can be associated with prolonged episodes [80]. Glimepiride may be associated with a lower incidence of hypoglycemia than glyburide [81]. α-Glucosidase inhibitors and thiazolidinediones should not induce hypoglycemia if used alone. Meglitinides use results in hypoglycemia probably similar to sulfonylureas' activity.

Diagnosis

The Whipple triad criteria may be used to diagnose hypoglycemia: symptoms consistent with hypoglycemia, low plasma glucose concentrations, and relief of symptoms after a carbohydrate load. Visually interpreted Chemstrips or portable glucometers can be used to detect hypoglycemia reliably in patients with diabetes and then to initiate treatment.

Clinical Manifestations

Adrenergic symptoms frequently encountered include sweats, palpitations, anxiety, tremors, and sensations of hunger or nausea. Neuroglycopenic symptoms include confusion, impaired concentration, weakness, blurred vision, difficulty

speaking, and drowsiness. Patients who are unable to recognize adrenergic symptoms (so-called hypoglycemia unawareness) may have serious neuroglycopenic symptoms of coma and seizures.

Treatment

Patients with diabetes should consider glucose levels less than 70 mg/dl (4 mmol/l) as hypoglycemic and requiring treatment [82–84]. Hypoglycemia should be treated quickly. In most patients, an oral glucose load of 15 g is generally recommended. This would increase glucose levels by 40 mg/dl (2.1 mmol/l) within 20 minutes. Patients should typically check glucose at the onset of hypoglycemia and 20 minutes after starting treatment. If plasma glucose levels did not increase by 20 mg/dl (1 mmol/L) at 20 minutes after treatment, then retreatment with another 15 g of glucose is recommended. Glucose gel is significantly slower in increasing blood glucose, and buccal use should not be recommended because absorption is minimal.

In the unconscious patient, glucagon, 1 mg subcutaneously or intramuscularly, will increase plasma glucose measurements significantly after 10 to 15 minutes, and levels may peak an hour later. A trained spouse or a support person typically administers glucagon at home. In the hospital setting, intravenous glucose administration of 25 g over several minutes (e.g., 50 ml of D50) followed by dextrose 10% infusion is the standard effective treatment. For recurrent or unresponsive oral agent–induced hypoglycemia, oral or intravenous diazoxide or octreotide subcutaneously could be used.

Hypoglycemia Unawareness

It is postulated that with repeated episodes of hypoglycemia, the nervous system adapts to low glucose levels and maintains glucose uptake despite hypoglycemia without adrenergic effects, leading to unawareness of hypoglycemia. Hypoglycemia unawareness may produce serious adverse events in patients with tight glycemic control. Previous episodes of hypoglycemia are essential for the development of hypoglycemia unawareness. Therefore, detection of episodes of hypoglycemia is important, especially nocturnal hypoglycemia, which is frequently not recognized.

Autonomic neuropathy leads to reduced epinephrine response to hypoglycemia and may contribute to development of severe hypoglycemia [77]. However, hypoglycemia unawareness may occur without autonomic neuropathy. Of note, glucagon response to hypoglycemia decreases with duration of diabetes.

Small studies showed that avoidance of hypoglycemia for days to months results in improvement of recognition of hypoglycemia or improved counterregulatory response (epinephrine and glucagon) to hypoglycemia. Therefore, aiming at higher glucose or hemoglobin A_{1c} goals and avoidance of hypoglycemia may improve hypoglycemia unawareness [85]. The use of caffeine or theophylline to stimulate the sympathetic–adrenal axis is of controversial clinical use.

Complications

In the DCCT, patients' neuropsychological tests did not distinguish between those treated with an intensive insulin regimen and those undergoing conventional therapy over the study's duration of 7 years, even in those patients who experienced episodes of coma or seizures. In small studies of children younger than 5 years, children with hypoglycemic seizures had poor results during neuropsychological testing [86], and therefore glucose goals should be relaxed to avoid severe hypoglycemia in children younger than 5 years. Furthermore, bedtime snacks are effective in reducing nocturnal hypoglycemia [87] and should be considered as part of the treatment protocol.

COMPLICATIONS OF DIABETES

Cardiovascular Disease

Epidemiology

Patients with diabetes are at more risk for developing cardiovascular disease than are patients without diabetes. Both men and women across all age groups with diabetes are at two to four times higher risk of death from cardiovascular disease. This increased risk is not, however, related solely to classic cardiac risk factors [88].

Etiology

Diabetes itself is an independent risk factor for development of cardiovascular disease, regardless of other risk factors. Plasma glucose levels predict development of cardiovascular disease in type 1 as well as type 2 DM. In the UKPDS, each 1% increase in hemoglobin A_{1c} was associated with 15% increase in the incidence of myocardial infarction (MI) [89]. Glucose elevations above the reference range also are associated with increased cardiovascular disease, even if they do not meet criteria for diagnosis of DM. This might be related to increased glycated end products and LDL oxidation. Traditional risk factors such as age, smoking, gender, hypertension, hyperlipidemia, and obesity play an important role in the development of cardiovascular disease of diabetes. Microalbuminuria is associated with a significant increase in cardiovascular events and might be a marker of an underlying progressive subclinical atherosclerosis [90]. Visual complications of DM, such as proliferative retinopathy, are also associated with cardiovascular disease. Obviously, retinopathy and microalbuminuria are not causal factors but might be indicators of other causal factors. Insulin resistance, as measured by "clamp" techniques or mathematical homeostasis model assessment, may be associated with cardiovascular events, as shown in several studies. The association, however, is weaker than the other risk factors already mentioned. In the UKPDS, the use of exogenous insulin was not associated with increased cardiovascular disease.

Diagnosis

Patients with diabetes in whom cardiovascular diseases develop may not initially have classic symptoms.

No evidence exists that cardiac tests perform differently in patients with or without diabetes, and therefore, the diagnostic approach should be similar to that with other populations without diabetes.

Prevention and Treatment

Glucose Control

In the UKPDS [36], treatment of overweight type 2 diabetes patients with metformin and intensively controlling glucose levels was associated with a 36% reduction in all-cause mortality. Therefore, metformin should be used as the drug of choice for patients with type 2 DM who are overweight. In the main UKPDS study, achieving tight control with insulin or oral agents was associated with a trend for reduced cardiovascular events, which did not initially reach statistical significance. However, in UKPDS 80 study, tight glucose control (A1c 7.9 vs. 8.5%) with insulin or oral agents was associated with reduced MI (13%) at 10 years of follow-up. Very tight glucose control was not associated with reduced cardiovascular disease (ADVANCE VADT and ACCORD studies [139-141]). It was associated with increased death rates in ACCORD study [139] (A1c 6.4%, short-term follow-up and use of TZD). Thiazolidinedione therapy is associated with reduced C-reactive protein and other markers of macrovascular

disease, independent of glycemic control. Pioglitazone efficacy in reducing a composite of all-cause mortality, nonfatal MI, and stroke in patients with DM and existing macrovascular disease was investigated in the "PROactive" study. The study did find a significant difference in this secondary combined outcome. The use of pioglitazone was associated with 16% reduction in that composite. However, these agents may precipitate congestive heart failure and can induce edema; furthermore, composite outcomes are different from a single outcome. Acarbose therapy in the STOP-NIDDM trial significantly reduced the risk of macrovascular disease and hypertension.

For type 1 DM, the DCCT demonstrated a nonsignificant reduction in cardiovascular disease events in patients treated with intensive insulin therapy. However, the DCCT follow-up study EDIC showed that intensive control (A1C 7.4%) is associated with reduced any CVD events.

Blood Pressure Control

Reducing blood pressure significantly reduces cardiovascular disease in patients with diabetes [92,93]. Evidence supports the use of ACE inhibitors and angiotensin receptor blockers as first-line therapy in individuals with diabetes. However, β-blockers, calcium-channel blockers, and diuretics may be safely used in patients with type 2 DM to reduce cardiovascular risk. The use of α-blockers in patients with diabetes to control blood pressure is controversial because of potentially increased numbers of cardiovascular events. Multiple studies addressed systolic blood pressure goals in epidemiologic studies: the lowest risk was seen in those with systolic blood pressure less than 120 mmHg. However, recent data from the ACCORD trial has not demonstrated improved CV outcomes with intensive systolic BP control (119 mmHg) versus conventional systolic BP control (133.5 mmHg) [91]. The American Diabetes Association consensus goal continues to be a systolic blood pressure less than 130 mmHg. Diastolic blood pressure control to less than 80 mmHg is desirable.

Aspirin

The use of aspirin has been shown in meta-analyses to reduce cardiovascular events similar to its effects in patients without diabetes, but use of aspirin should be gauged carefully to balance potential risk for bleeding. Doses of 75 to 325 mg/d have been effective. The American Diabetes Association recommends aspirin therapy for patients with diabetes requiring secondary prevention and in men over 50 and women over 60 with additional CV risk factor(s) for primary prevention.

Lipid Control

Evidence exists to support LDL reduction by using a "statin" in preventing cardiovascular disease in diabetes patients without cardiovascular disease (CARDS study) and in diabetes patients for secondary intervention [94–96]. The recommended goal is LDL less than 100 mg/dl (2.6 mmol/l). Modest reduction in triglycerides levels with a fibrate (122 vs. 144 mg/dl, 1.38–1.63 mmol/l) was not associated with a reduction in cardiovascular disease events in the ACCORD study [139].

Thrombolysis

Thrombolytic therapy has been shown to reduce mortality after acute MI in individuals with diabetes without increased risk of hemorrhage compared with findings in the general population. Thrombolytic therapy should not be withheld because of concern about retinal hemorrhage in patients with retinopathy. However, the same contraindications for the use of thrombolysis in the general population apply to the population with diabetes.

Angioplasty for Acute Myocardial Infarction
Primary angioplasty was shown to be successful in patients with DM and may be superior to thrombolysis in patients with MI.

Postinfarction Insulin
The use of intensive insulin treatment after MI may reduce mortality in type 2 DM by 29% [97] in certain populations. Although post-MI insulin use may reduce mortality, it does not prevent recurrent MI.

β-Blockers
The use of β-blockers in patients with DM after MI is not contraindicated, and β-blockers should be considered for all patients after MI, including patients with diabetes.

ACE Inhibitors
Using an ACE inhibitor within the first 2 days after MI for at least 4 weeks reduces mortality, especially in patients who are at high risk, such as those with intercurrent congestive heart failure. For this reason, ACE inhibitors should be used in patients while serum potassium levels and renal status are being monitored.

Antiplatelet Therapy
Adding clopidogrel to aspirin reduces the risk of stroke and fatal as well as nonfatal MI by 20% in patients with symptoms of acute coronary syndromes. However, risk of bleeding should be balanced.

Coronary Bypass
Patients with DM are at increased risk of surgical complications, restenosis, and death after coronary bypass graft. This increased risk may be secondary to associated diffuse arthrosclerosis, diabetic cardiomyopathy, or renal disease. However, the Bypass Angioplasty Revascularization Investigation demonstrated that coronary bypass using the internal mammary artery was superior to angioplasty [98]. Therefore, in patients with DM and multivessel disease, coronary artery bypass graft is recommended over angioplasty.

Stents
Patients with DM undergoing angioplasty should use stents and receive antiplatelet therapy. Use of stents improves outcome in comparison with angioplasty without stents.

Eye Disease

Etiology
Visual impairment in patients with diabetes is mainly secondary to retinopathy and cataracts. The most important risk factor for the development of progressive retinopathy in type 1 or type 2 DM is glucose control, measured as glycated hemoglobin. Other factors include hypertension, duration of diabetes, elevated triglyceride levels, total cholesterol, low HDL cholesterol, and pregnancy. Smoking and alcohol use, however, are not considered risk factors for retinopathy.

Pathophysiology
Loss of vision in type 1 DM is most likely associated with proliferative retinopathy (80%), but in type 2 DM, it is most likely secondary to macular edema. Development of new vessels and glial proliferation in the retina may result in hemorrhage, macular distortion, and retinal detachment, leading to visual loss. Reduced capillary profusion and ischemia break the blood–retinal barrier with resultant fluid leakage, edema, endothelial proliferation, formation of microaneurysms, thickening of the retinas, and neuronal necrosis.

Multiple types of retinal lesions develop in patients with DM secondary to the process mentioned.

Epidemiology

The prevalence of legal blindness in the population of individuals with diabetes in southern Wisconsin was 3.6% in type 1 DM and 1.6% in type 2 DM. In type 1 DM patients, 20% had impaired vision 30 years after the diagnosis of diabetes, whereas 35% of type 2 DM patients had impaired vision 20 years after diagnosis. The estimated incidence of blindness is 3.3 per 100,000 annually.

Diagnosis

Screening by using direct ophthalmoscopy and retinal digital photography is effective at detecting unrecognized retinopathy. More than one-third of patients with type 2 DM have retinopathy at diagnosis, and therefore, annual screening examinations are recommended for all patients with type 2 DM, starting at the time of diagnosis. In type 1 DM, retinopathy develops after the onset of puberty, and therefore, screening should start at age 12, or if the disease is diagnosed after puberty, then 3 years after diagnosis.

Prevention and Treatment

Glucose Control

The DCCT demonstrated that intensive management control of glucose prevents the development or progression of retinopathy in type 1 DM (76% primary prevention and 54% secondary prevention) compared with less-tight control [11]. Other studies provided similar results [36]. Several studies reported a transient deterioration of retinopathy with acute control, usually lasting several months. Therefore, if severe retinal disease or visual loss exists, eye disease should be treated before rapid control of glucose. In type 2 DM, tight glucose control (UKPDS) resulted in reduced retinopathy by 20% to 25% as well as reduced surgical intervention; in addition, early tight control is not associated with transient deterioration of retinopathy, and reducing hemoglobin A_{1c} to 7% is likely to reduce eye disease (UKPDS). In addition, tighter glucose control was associated with reduced retinopathy in one large study but did not affect vision loss (ACCORD). However, death rates were increased in this study.

Blood Pressure Control

Control of blood pressure to target reduces the rate of progression of retinopathy and progression to visual loss by 50% in people with type 1 DM [99] and by 30% in those with type 2 DM (UKPDS). The effect is noted earlier than effects of blood glucose control and is not related to the use of a special blood pressure agent. Both β-blockers and ACE inhibitors were similarly effective. These conclusions are also likely to be valid for patients with type 1 DM. Tight blood pressure control in type 2 DM patients to less than 120 systolic versus less than 140 systolic such as in ACCORD study was not associated with better retinal outcomes.

Antiplatelet Therapy

Use of aspirin with or without dipyridamole versus ticlopidine reduced microaneurysm formation in early retinopathy but did not prevent the development of high-risk proliferative retinopathy or cataract formation as noted in the Early Treatment Diabetic Retinopathy Study (ETDRS). Aspirin did not increase the risk of vitreous hemorrhage; therefore, aspirin is not contraindicated in patients with diabetes and retinopathy.

Aldose Reductase Inhibitors
Theoretically, the use of aldose reductase inhibitors may reduce tissue damage and oxidative stress as well as glycated end products. In clinical trials, however, these agents did not show an effect on slowing the progression of retinopathy.

Laser Photocoagulation
In diabetic proliferative retinopathies, scatter photocoagulation significantly reduced progression of disease and was associated with reduced new-vessel formation and reduced visual loss by 50%. ETDRS studied patients with proliferative diabetic retinopathy in at least one eye or severe nonproliferative diabetic retinopathy in both eyes and studied the photocoagulation effects [100–102]. ETDRS showed a significant reduction of sudden visual loss or vitrectomy; therefore, scatter laser treatment is recommended for patients with proliferative diabetic retinopathy [103]. No clear-cut evidence indicates that patients with mild or moderate nonproliferative eye disease would benefit from photocoagulation. However, patients with type 2 DM or older patients with DM who are older than 40 years with severe nonproliferative diabetic retinopathy would benefit from photocoagulation [104].

Macular edema is treated with focal photocoagulation even before visual acuity is affected and regardless of the severity of nonproliferative diabetic retinopathy. This mode of therapy reduces future visual loss.

Vitrectomy
In type 1 DM, early vitrectomy results in reduction of visual loss by 10% in patients who have persistent vitreous hemorrhage when compared with delayed vitrectomy (1 year later) over a period of 4 years. This is not the case in patients with type 2 DM, in whom early and delayed vitrectomy have similar outcomes. In patients with tractional retinal detachment or severe fibrovascular proliferation and reduced visual acuity, early vitrectomy reduced sudden visual loss by 15.9% over a 4-year period.

Diabetic Neuropathy

Classification
The most common form of diabetic neuropathy is distal symmetric polyneuropathy. Another common form is mononeuropathy, such as carpal tunnel syndrome, ulnar neuropathy, peroneal neuropathy, or cranial nerve neuropathies. Less common are radiculopathies, such as diabetic lumbar plexopathy and intercostal (truncal) radiculopathy. Autonomic neuropathy usually involves multiple systems and may present with gastroparesis, hyperhidrosis, anhidrosis, or bladder dysfunction.

Pathophysiology
Several hypotheses explain the pathophysiology of diabetic neuropathy. Increased glycols influx in Schwann cells through the aldose reductase system leads to depletion of sodium/potassium adenosine triphosphatase and slowing of nerve-conduction velocities. Advanced glycation of essential nerve proteins also leads to several pathologic changes and is postulated to result in neuropathy. Ischemia secondary to microvascular damage results in multifocal loss of exons. Finally, it is thought that a deficiency of nerve growth factors and other trophic factors in diabetes increases neuropathy.

Epidemiology
Prevalence of neuropathy is estimated around 34% in type 1 and 26% in type 2 DM [105]. Neuropathy may occur early in the disease, especially with suboptimal glycemic control. In the DCCT, clinically detectable neuropathy developed in 10% after 5 years of enrollment. In type 2 DM, the incidence is around 6% per year.

Diagnosis

Clinical Manifestations

The history and physical examination—including sensory testing and evaluation of light touch, pinprick perception, thermal sensitivity, and vibration sensation by using a 128Hz tuning fork—provide adequate information for diagnoses. The use of monofilament as a screening tool should not replace the neurologic examination, although it has been widely accepted as a reliable method.

Sensory loss, paresthesia, neuropathic pain, autonomic abnormalities, and motor weakness are prominent symptoms.

Laboratory Findings

Several tests are used for the diagnosis of diabetic neuropathy. In the Rochester Diabetic Study, the most sensitive tests were nerve-conduction studies and autonomic testing by using heart rate (i.e., R-R interval) change during the Valsalva maneuver [106]. Quantitative sensory threshold tests were less sensitive in diagnosing neuropathy, but combination thermal and vibration sensory thresholds provide high sensitivity and specificity.

Sural Biopsy

Small-nerve biopsy should not be a diagnostic tool because of the associated morbidity, pain, and invasiveness.

Treatment

Currently, no pharmacologic therapeutic modalities reverse or cure diabetic neuropathy. Treatment is focused on pain control.

Glucose Control

With intensive therapy, clinically detectable neuropathy is reduced in patients with type 1 DM (DCCT findings) and to a lesser extent in type 2 DM (UKPDS).

Aldose Reductase Inhibitors

These agents reduce the accumulation of sorbitol in nerve cells. Meta-analysis demonstrated some benefits for motor neuropathy, but generally these are associated with adverse effects and no demonstrable efficacy with autonomic or sensory neuropathy [107].

Tricyclic Antidepressants

This class is considered a first-tier therapy [108]. Amitriptyline is useful in the treatment of painful polyneuropathy, but its use is limited because of the adverse-effect profile and sedation. Nortriptyline and desipramine may also be used for the same indication and are associated with lower levels of sedation. Tricyclic antidepressants are also useful for the treatment of pain secondary to lumbar plexopathy.

Duloxetine

This is another first-tier therapy. In two randomized studies, duloxetine was effective in reducing pain scores. A dose of 60 mg daily is safe and effective in reducing pain, even in patients older than 65 years. Side effects include constipation and somnolence.

Pregabalin

Pregabalin also is considered first-tier therapy. In randomized double-blind studies, this agent was effective in doses of 300 to 600 mg daily. Side effects include dizziness, somnolence, and edema.

Other Agents
Oxycodone, gabapentin, venlafaxine, lamotrigine, tramadol, carbamazepine, and capsaicin [108–110] are effective in controlling painful neuropathy by 25% to 50% compared with placebo.

Surgery
Surgical decompression reverses entrapment neuropathies such as carpal tunnel syndrome. Other entrapment neuropathies have less successful outcomes with surgery.

Renal Disease

Definition
Microalbuminuria is one of the earliest manifestations of diabetic renal disease, characterized by increased secretion of albumin greater than 30 mg/d. Diabetic nephropathy is an advanced stage of diabetic renal disease in which albumin excretion is more than 300 mg/d.

Etiology
Glycation end products and sorbitol interaction with growth factors and structural proteins lead in the presence of altered hemodynamic process to glomerular lesions that progress in a predictable pattern, leading to impaired renal function.

Pathophysiology
Early in the course of DM, increased glomerular volume and glomerular capillary pressure lead to increased glomerular filtration rate and kidney size. With progression of diabetes, the basement membranes of the glomerulus, tubules, and the Bowman capsule thicken. This is followed by mesangial expansion and accelerated damage of arterioles, as well as reduced filtration rates. This process progresses to diffuse glomerular sclerosis. Kimmelstiel-Wilson nodular lesions are present in 20% of renal biopsies of patients with diabetes.

Epidemiology
The cumulative incidence rate of diabetic nephropathy is 30% at 30 years of duration of diabetes. In types 1 and 2 DM, the prevalence of microalbuminuria is variable and depends on multiple factors such as duration of diabetes, hypertension, smoking, and hyperlipidemia. The average time for progression from microalbuminuria to diabetic nephropathy in type 1 DM is around 8 years [111]. Overall incidence of developing end-stage renal disease in patients with type 1 DM regardless of albuminuria is 14% over a period of 10 years. It is estimated that up to 50% of type 1 DM patients with diabetic nephropathy will develop end-stage renal disease after 10 years.

In type 2 DM, the cumulative incidence is estimated at around 25% at 20 years of duration of diabetes. However, a significant proportion (8%) may have microalbuminuria at diagnosis. In fewer than 0.5% of patients with type 2 DM without proteinuria, end-stage renal disease develops within 10 years, but in 8% to 10% with baseline proteinuria, end-stage renal disease develops during the same period.

Diagnosis
The standard urine dipstick is not sensitive to measure albumin less than 300 mg/24 hr. The best test is radioimmunoassay measurement of microalbumin in a 24-hour urine sample. However, 4-hour, 12-hour, and overnight collections achieve similar results (95% correlation). Albumin concentration measurements from spot urine are also a useful diagnostic test and are becoming the standard of care, especially if coupled with creatinine as the albumin-to-creatinine ratio. Special microalbumin dipsticks are of variable sensitivity and specificity, and therefore, depending on the amount of urine dilution, these tests would provide variable results and are not as

reliable as the standard tests. The use of the albumin/creatinine ratio compensates for urine dilution with a high sensitivity and specificity.

In type 1 DM, minor elevations in blood pressure precede diabetic nephropathy by years. No role exists for kidney biopsy in diagnosing diabetic nephropathy in patients with elevated urine microalbumin and a typical history as well as diabetic retinopathy. Nearly all (>98%) biopsies performed in patients with type 1 DM indicate diabetic nephropathy, especially if the patient has prolonged duration of diabetes (>5 years) in the absence of a clinically apparent secondary cause.

In type 2 DM, hypertension precedes diabetic nephropathy by years. Frequently, proteinuria is present at diagnosis. Approximately 12% to 20% of all renal biopsies performed on patients with proteinuria in patients with type 2 DM are due to nondiabetic etiology. Biopsy could be considered if the duration of diabetes is short in the absence of retinopathy.

Estimates of glomerular filtration rate (eGFR) has become another important method to diagnosis chronic kidney disease. Chronic kidney disease is defined as eGFR <60 ml/min for at least 3 months. Calculations of eGFR are a more accurate gauge of kidney function than use of serum creatinine alone.

Prevention and Treatment

Glucose Control

In the DCCT/EDIC, patients who achieve tight glycemic control reduce the risk of development of microalbuminuria by 39% and the progression of albuminuria by 54%, although the conventionally treated group reported 6.5% increase in albumin excretion per year. In the UKPDS, tight control leads to a 33% relative risk reduction for the development of microalbuminuria on the long term and recently, ADVANCE study [141] showed that very tight glucose control reduces nephropathy; therefore, tight glucose control is recommended in type 1 and type 2 DM patients to reduce the development of renal disease and progression of existing microalbuminuria. It should be noted, however, that a substudy of the ACCORD trial [139] did not show evidence that very tight control in the short term reduces nephropathy, nor did the VADT study [140].

Blood Pressure Control

Meta-analysis of several studies on the effect of blood pressure control on proteinuria demonstrated that a 10-mm Hg decrease in blood pressure by using ACE inhibitors was adequate to show a significant reduction of proteinuria. In the UKPDS, intensive blood pressure control to less than 144/82 mm Hg was compared with conventional control to less than 154/87 mm Hg, which led to 8% absolute risk reduction of microalbuminuria over a 6-year period [112,113]. Very tight blood pressure control, however, may not improve cardiovascular death rates.

In type 1 DM, patients with nephropathy whose main arterial pressure was 6 mm higher than the treated group tripled their urine microalbumin excretion over a 2-year period. Therefore, blood pressure control is important in controlling albuminuria and nephropathy.

ACE Inhibitors

ACE inhibitors function by reducing blood pressure as well as glomerular pressure and appear to be effective in delaying the progression of proteinuria in both type 1 [114,115] and type 2 DM [114]. ACE inhibitors decrease microalbuminuria and are effective in reducing diabetic nephropathy and delaying the progression toward end-stage renal disease.

Angiotensin Receptor Blockers

Evidence supports the use of these agents in patients with type 2 DM [115]. Combining ARBss with maximal doses of ACE inhibitors may further reduce blood pressure

(modestly) and albuminuria. However, results from the ONTARGET study that compared telmisartan, ramipril, or both in people with high vascular risk showed that both agents are effective at improving renal outcomes, but the combination worsened overall renal outcomes with no additional reduction in CV events [116].

Aldosterone Inhibitors
A small dose of spironolactone, 25 mg/d, or eplerenone added to an ACE inhibitor reduced albuminuria significantly (40%).

Protein Restriction
A high-protein diet leads to hyperfiltration, and therefore, it is not advised in patients with DM. Protein restriction was also shown to reduce the decline in glomerular filtration rate in a meta-analysis of smaller studies [117].

INTENSIVE GLYCEMIC MANAGEMENT

Definition
Intensive glycemic management indicates tight control of blood glucose, aiming at near normal blood glucose measurements. In patients with type 1 DM, this is achieved with multiple daily insulin injections or insulin pumps (continuous subcutaneous insulin infusions) and is also known as intensive insulin therapy or flexible insulin therapy. In patients with type 2 DM, tighter control may be achieved with oral agents (at least for the short term), or combination oral agents and insulin, or with multiple daily insulin injections.

Etiology/Rationale
The significant long-term benefits noted with large studies, the DCCT (type 1 DM) and UKPDS (type 2 DM), were associated with tighter glucose control. This is the basis for recommending intensive glycemic management.

In the fasting state, the human pancreas secretes insulin continuously, which prevents lipolysis and other catabolic activities; this is referred to as basal insulin. During eating, insulin levels increase immediately and stay elevated for 1 to 4 hours. This meal-related insulin production is proportional to the amount of the carbohydrate in the meal and constitutes approximately 50% of the total daily insulin release. Intensive insulin therapy means providing a continuous supply of insulin to mimic natural pancreatic basal secretion and also providing meal insulin in doses according to the size of the meal to mimic natural pancreatic insulin secretion. Because meal timing (and therefore insulin) is variable and flexible, this regimen is also referred to as flexible insulin therapy.

Outpatient Setting
Refer to previous sections on type 1 and type 2 for additional discussion.

Type 1 DM
The DCCT and other studies showed that intensive glycemic control can be achieved by MDI by providing short-acting insulin to cover meals; however, short-term insulin use was accompanied by hypoglycemia [118] and also by postprandial hyperglycemia. The very-rapid-acting insulin analogues increase rapidly after injection and may better control postprandial hyperglycemia [119,120]. These agents have a short duration of action and therefore better mimic natural insulin meal release. Therefore very-rapid-acting insulin analogues are used frequently as meal insulins. Insulin preparations used in the DCCT/MDI regimen to cover basal insulin were either intermediate-acting or long-acting Ultralente. Their peak activity was also associated with nocturnal hypoglycemia. Glargine, which does not exhibit peaks or troughs, is widely used in practice now to provide basal insulin around the clock and is used frequently as basal insulin in the

MDI program [121,122]. The evidence obtained from the DCCT and other studies [123] supports the use of intensive insulin therapy to achieve near-normal A_{1C} percentage through MDI or insulin infusions. The use of pramlintide as an adjunctive agent may provide an additional (but small) improvement to glycemic control [124].

Type 2 DM

The UKPDS showed that adequate glucose control can be achieved by using oral agents; however, this is dependent on beta cell function, which declines over a short period, resulting in adding a second oral agent and insulin. Evidence supports the use of dual agents to achieve adequate glucose control, but a significant number of patients (40%) would require insulin over a period of several years. Combining insulin and oral agents is also effective and safe. The evidence from the UKPDS supports the use of antidiabetic agents to achieve a near-normal A_{1C} percentage with metformin, sulfonylureas, insulin, or combination therapy. The use of pramlintide as adjunctive therapy adds little to the degree of control, and it is not indicated to be used as a stand-alone agent [125]. Exenatide, conversely, may provide an additional (but small) improvement in glycemic control [126]. Acarbose could be used and may have an additional benefit of reducing the risk of hypertension and cardiovascular events, but patients frequently discontinue using this agent because of side effects [127]. Of interest are the findings of ACCORD, VADT, and ADVANCE trials [139–141] showing that very tight control of blood glucose may not have an additional benefit or even increase death rates (ACCORD [139]). As such, attempts to control blood glucose in type 2 DM to normal levels are not supported by evidence.

The Inpatient Setting

Epidemiology

People with DM are frequently (25% annual rate) admitted to the hospital and on average stay longer than those without DM. Hospital mortality rates are higher for patients with hyperglycemia, even if they are not diagnosed with DM [128].

Pathophysiology

During hospitalization, glycemic control in patients with DM becomes a significant problem because of anorexia, frequent episodes of fasting for tests, reduced activity, newly prescribed medications (especially corticosteroids), intravenous glucose infusions, parenteral nutrition, inappropriate timing of meals, and most important, stress of illness or surgery. These factors may lead to excessive hyperglycemia or serious hypoglycemia if antidiabetic therapy is not adjusted. Furthermore, in patients without DM, high glucose values may develop secondary to acute illness.

Hospitalized patients are at increased risk for severe hypoglycemia, which may result in coronary events, arrhythmias, and seizures, and are also at increased risk from severe hyperglycemia including dehydration, ketoacidosis, hyperosmolar coma, increased infection rates, impaired immune function [129], and increased mortality [130–132]. Evidence supports avoidance of excessive hyperglycemia in hospitalized patients at risk for infection [133]. However, the use of intensive insulin therapy to prevent sepsis is not supported [134].

Mortality Rates

Although initial studies suggested that intensive insulin therapy may be associated with reduced hospital mortality, recent meta-analysis [134] does not support that finding. As such, the effect of intensive insulin therapy use on mortality is neutral, both in the ICU setting and non-ICU setting. The multicenter Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation (NICE–SUGAR) study showed an increase in mortality rates, while earlier studies showed a benefit [135,136].

Myocardial Infarction
The use of insulin infusion in acute MI in patients with hyperglycemia was thought to be associated with survival benefits following the DIGAMI study. Subsequent studies [134] did not confirm this intervention.

Critical Illness
The use of insulin infusion to achieve tight glucose control is associated with a sixfold increase in hypoglycemia. Hypoglycemia in the medical ICU is associated with increased mortality and increased (prolonged) hospitalization.

Glucose Targets
Lacking adequate data, the general recommendations are based on epidemiologic and short-term small studies [134] of glycemic targets. The general principles are to avoid hypoglycemia. In the ICU, the lower-threshold glycemic target is 140 mg/dl. The upper threshold is controversial, with recommendations of 180 to 200 mg/dl [137].
Patients Taking Oral Medications. Oral antidiabetic medications are usually stopped the day of surgical intervention and resumed once oral food intake is established. Frequently, metformin is not resumed until actual hospital dismissal because of its potential for severe adverse events in patients who may be dehydrated, undergo surgical intervention, or use contrast material for radiologic tests. Thiazolidinediones are safe in patients with mild renal impairment but may predispose to edema and congestive heart failure and are frequently stopped during hospitalization. Meglitinides, which have a shorter duration of action, may be safer to use than sulfonylureas. However, both meglitinides and sulfonylureas can be used in the stable hospitalized type 2 DM patient with caution to avoid hypoglycemia. As a replacement, insulin is used for the short term.
Patients Using Insulin. Patients with type 1 DM must have some form of insulin at all time. Patients with type 2 DM can delay insulin injection till after the procedure, if the procedure is short (e.g., endoscopy) and does not interfere with meal timing (e.g., early morning procedure). In most situations of surgical interventions and during severe illness and hospitalization, insulin is provided in a reduced dose to avoid hypoglycemia but in a way to continue adequate control.

In most situations, the patient is fasting, and then meal insulin is discontinued before any intervention, and only basal insulin is provided (1/2–2/3 dose of NPH or full-dose long-acting insulin analogue) until the patient recovers and is able to eat. In patients who have a complicated hospital course, further adjustments of the original regimen are needed. Frequently, during an illness, the insulin dose provided is higher than the prehospitalization dosage.

Intravenous Infusion
Continuous intravenous insulin infusion is being used frequently especially for critically ill patients [133–135,137]. The use of insulin infusions in non-ICU patients is generally not supported by evidence as the only method of treatment [134].Several protocols are available, and no evidence suggests the superiority of one regimen to another.

Insulin Sliding Scale
The use of a sliding scale is unfortunately widespread and is frequently (>25%) the cause of episodic hypoglycemia and excessive hyperglycemia. Sliding scales could be useful if basal insulin or (oral agent) were provided and if sliding scales were adjusted quickly to each individual patient [138]. As such, if sliding scales are used, they should be used for a short period only. Initiating basal plus bolus insulin as soon as possible is associated with better glucose control.

REFERENCES

Type 1 Diabetes Mellitus

Etiology, Epidemiology, and Diagnosis

1. (2) **McKinney PA** et al. Perinatal and neonatal determinants of childhood type 1 diabetes. Diabetes Care 1999;22:928–932.

   In this case-controlled study, a higher frequency of neonatal infections was noted to be a risk factor for subsequent development of type 1 DM. Other factors including having a mother with type 1 DM, having an older mother, and preeclampsia during pregnancy were risk factors for the development of diabetes.
2. (2) **Dahlquist G** et al. The epidemiology of diabetes in Swedish children 0–14 years: A six-year prospective study. Diabetologia 1985;28:802–808.

   In this case-controlled study, hospital records of 892 patients with type 1 DM were compared with those of 2,291 controls. Different perinatal events were noted to increase the risk of type 1 DM, including maternal–child blood group, birth stress with cesarean section, and infectious diseases.
3. (4) **Van Belle** et al**.** Type 1 Diabetes: Etiology, immunology, and therapeutic strategies Physiol Rev 2011;91:79–118.

   In this review, the authors review through important studies related to the genetic basis of type 1 DM.
4. (2) **Molbak AG** et al. Incidence of insulin-dependent diabetes mellitus in age groups over 30 years in Denmark. Diabet Med 1994;11:650–655.

   In this historical prospective study cohort of nearly 1 million Danish subjects, 16.2% used insulin for treatment of type 1 DM.
5. (2) **Verge CF** et al. Number of autoantibodies (against insulin, GAD or ICA512/IA2) rather than particular autoantibody specificities determines risk of type I diabetes. J Autoimmun 1996;9:379–383.

   In this study, insulin antibodies, GAD antibodies, and ICA 512 antibodies were measured in 45 subjects newly diagnosed with type 1 DM, 882 first-degree relatives, and 217 control subjects. ICA 512 antibodies were measured in 45 subjects newly diagnosed with type 1 DM, 882 first-degree relatives, and 217 control subjects. The number of positive antibodies rather than the particular antibody predicted type 1 DM.
6. (2) **Ziegler AG** et al. Autoantibody appearance and risk for development of childhood diabetes in offspring of parents with type 1 diabetes: The 2-year analysis of the German BABYDIAB Study. Diabetes 1999;48:460–468.

   This prospective cohort multicenter follow-up study was undertaken to establish the role of autoantibodies in type 1 DM in children of patients with diabetes. A population of 1,353 children was recruited immediately after birth in 1998, and 114 children completed 4-year follow-up testing. Results at birth indicated that none of the children produced autoantibodies except those that had been acquired from their mothers. Antibodies detected at 9 months were present at 2 years. At 2 years, antibodies appeared in 11% of children and 3.5% of children who had more than one antibody. IAAs were most frequently detected and were usually the first antibodies to appear in the circulation. Cumulative risk for type 1 DM at 5 years was 1.8% and was 50% for those children who possessed more than one antibody at the age of 2 years. Diabetes developed in only nine children during the study.
7. (3) **Kulmala P** et al. Prediction of insulin-dependent diabetes mellitus in siblings of children with diabetes: The Childhood Diabetes in Finland Study Group. J Clin Invest 1998;101:327–336.

   In this observational population-based study, combined screening with GAD and IA-2 protein autoantibodies identified 70% of those testing positive in the histochemical ICA test. This study illustrates the difficulties in securing a diagnosis of type 1 DM predisposition through measurement of autoantibodies.
8. (2) **Vardi P** et al. Predictive value of intravenous glucose tolerance test insulin secretion less than or greater than the first percentile in islet cell antibody positive relatives of type 1 (insulin-dependent) patients with diabetes. Diabetologia 1991;34:93–102.

   In this study of a high-risk population, in 15 of 17 subjects with intravenous glucose tolerance test scores below the first percentile, type 1 DM developed, whereas in 3 of 18 with intravenous glucose tolerance test results higher than the first percentile, diabetes developed ($p = 0.001$; OR, 38). The negative predictive value of an intravenous glucose tolerance test result higher than the first percentile was 83%.

9. (1) **Diabetes Prevention Trial: Type 1 Diabetes Study Group**. Effects of insulin in relatives of patients with type 1 diabetes mellitus. N Engl J Med 2002;346:1685–1691.

This randomized controlled multicenter nonblinded clinical trial studied the effect of injectable insulin in preventing DM in relatives of patients with type 1 DM. Of 84,228 first- and second-degree relatives of patients with type 1 DM, 372 subjects tested positive for multiple antibodies, projecting an increased risk for future diagnosis of type 1 DM. Three hundred thirty-nine of three seventy two subjects were randomly assigned to receive low-dose subcutaneous Ultralente insulin twice-daily injections and insulin infusion over a period of 4 days once yearly or to undergo observation. DM developed in 69 subjects in the treated group versus 70 subjects in the observation group, indicating no role for injectable insulin for preventing type 1 DM.

10. (31) **Yu L** et al. Diabetes Prevention Trial 1: Prevalence of GAD and ICA512 (IA-2) autoantibodies by relationship to proband. Ann N Y Acad Sci 2002;958:254–258.

In this study among children of whom both parents had DM, the prevalence of autoantibodies was 8.6%, and in single parents with diabetes, the prevalence was 4%. The children of fathers with diabetes had higher antibody prevalence than the children of mothers with diabetes.

Treatment

11. (1) **The Diabetes Control and Complications Trial Research Group**. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977–986.

This was a prospective randomized multicenter study with primary end points of microvascular and macrovascular complications. Mean follow-up was 6.5 years. To evaluate the efficacy of intensive insulin therapy in preventing long-term complications in 1,441 patients with type 1 DM, nearly half had no evidence of retinopathy (primary prevention cohort). Patients were assigned to receive intensive insulin with three or more daily injections or insulin pump compared with another group assigned to conventional therapy of daily insulin injections. Intensive insulin therapy reduced the mean risk for developing retinopathy by 76% in the primary prevention group and 54% in the secondary prevention cohort. Intensive insulin therapy reduced microalbuminuria by 39% and proteinuria by 54%. Neuropathy was reduced by 60%. Macrovascular disease end points were not statistically different between the two groups. The most adverse events noted were a twofold to threefold increase in severe hypoglycemia in the arm that received intensive insulin treatment.

12. (1) **Lawson ML** et al. Effect of intensive therapy on early macrovascular disease in young individuals with type 1 diabetes. Diabetes Care 1999;22(suppl 2):B35–B39.

In this meta-analysis of six studies on the effect of intensive insulin treatment on macrovascular disease in patients with type 1 DM, no significant effect was noted on the number of patients in whom cardiovascular events developed or on mortality rates from cardiovascular disease.

13. (1) **Egger M** et al. Risk of adverse effects of intensified treatment in insulin-dependent diabetes mellitus: A meta-analysis. Diabet Med 1997;14:919–928.

In this meta-analysis of 14 studies, 1,028 patients were allocated to intensified insulin treatment and 1,039 patients to conventional treatment. The risk of severe hypoglycemia was mainly due to glycemic goals, as determined by the degree of normalization of glycemia.

14. (1) **DCCT.** Effect of intensive therapy on the microvascular complications of type 1 diabetes mellitus. JAMA 2002;287:2563–2569.

The writing team of the DCCT summarized the results of the DCCT cohort and succeeding follow-up of 7 years in this article, which indicated that intensive insulin should be started early to reach a goal of hemoglobin A_{1c} less than 7%.

15. (1) **Gale EA**. A randomized, controlled trial comparing insulin Lispro with human soluble insulin in patients with type 1 diabetes on intensified insulin therapy: The UK Trial Group. Diabet Med 2000;17:209–214.

In this randomized double-blind crossover study of 12 weeks duration, 93 patients used MDIs of lispro or regular insulin. NPH insulin was used in both these groups. Lispro insulin was as effective as regular insulin in achieving glycemic control.

16. (1) **Pickup J** et al. Glycaemic control with continuous subcutaneous insulin infusion compared with intensive insulin injections in patients with type 1 diabetes: Meta-analysis of randomised controlled trials. BMJ 2002;324:705.

This meta-analysis reviews the effects of two different modalities of insulin treatment on glycemic control. Insulin infusion controls blood glucose better than multiple daily injections, but the differences are few.

17. (2) **Tsui E** et al. Intensive insulin therapy with insulin Lispro: A randomized trial of continuous subcutaneous insulin infusion versus multiple daily insulin injection. Diabetes Care 2001;24:1722–1727.

    In this randomized trial, 27 patients were enrolled to receive either MDIs or insulin effusions. The results were similar in relation to glycemic control and quality of life.

18. (1) **Davey P** et al. Clinical outcomes with insulin Lispro compared with human regular insulin. Clin Ther 1997;19:656–674.

    In this meta-analysis, insulin lispro was compared with regular insulin for outcome events. Results showed that glucose control is better with lispro and without concurrent increase in hypoglycemia.

19. (2) **Heller SR** et al. Effect of the fast-acting insulin analog Lispro on the risk of nocturnal hypoglycemia during intensified insulin therapy. Diabetes Care 1999;22:1607–1611.

    One hundred sixty-five patients with type 1 DM participated in this randomized crossover open-label study with either lispro regular insulin. Glycemic control was equal for both groups. More hypoglycemia episodes occurred with regular insulin.

20. (1) **Zinman B** et al. Effectiveness of human Ultralente versus NPH insulin in providing basal insulin replacement for an insulin Lispro multiple daily injection regimen: A double-blind randomized prospective trial. Diabetes Care 1999;22:603–608.

    In this double-blind randomized clinical trial, Ultralente was compared with NPH as basal insulin in 178 patients. At the end of the study, higher doses of Ultralente were needed to achieve glycemic control. The study suggests that NPH might be superior to Ultralente, but this is a function of the methods in the study, and different management of Ultralente injections might yield different results.

21. (1) **Riddle MC** et al. The treat-to-target trial: Randomized addition of glargine or human NPH insulin to oral therapy of type 2 patients with diabetes. Diabetes Care 2003;26(11):3080–3086.

    Majority of patients (~60%) attained HbA(1c) less than or equal to 7% with each insulin type. However, nearly 25% more patients attained this without documented nocturnal hypoglycemia (≤72 mg/dl [4.0 mmol/l]) with glargine (33.2 vs. 26.7%, $p < 0.05$). Moreover, rates of other categories of symptomatic hypoglycemia were 21% to 48% lower with glargine.

22. (2) **Gilbertson HR** et al. The effect of flexible low glycemic index dietary advice versus measured carbohydrate exchange diets on glycemic control in children with type 1 diabetes. Diabetes Care 2001;24:1137–1143.

    Flexible dietary instructions with an emphasis on low-glycemic-index foods improved hemoglobin A_{1c} levels when compared with the standard carbohydrate exchange diet in this randomized, prospective, parallel study of 104 subjects over a 12-month period. The difference in hemoglobin A_{1c} was 8.05 versus 8.61 ($p = 0.05$).

23. (2) **Landt KW** et al. Effects of exercise training on insulin sensitivity in adolescents with type I diabetes. Diabetes Care 1985;8:461–465.

    The effects of exercise were studied in nine patients with type 1 DM and six controls. After 12 weeks, significant increases in insulin sensitivity, maximal oxygen uptake, and lean body mass were noted. No significant change was seen in glycated hemoglobin.

24. (2) **Schiffrin A, Parikh S.** Accommodating planned exercise in type I patients with diabetes on intensive treatment. Diabetes Care 1985;8:337–342.

    In this interventional study, 13 type 1 DM patients receiving intensive insulin were asked to exercise after injecting their insulin. A significant decrease in blood glucose levels of 60 mg/dl was noted reaching a nadir at 45 minutes.

Type 2 Diabetes Mellitus

Etiology

25. (2) **Brancati FL** et al. Body weight patterns from 20 to 49 years of age and subsequent risk for diabetes mellitus: The Johns Hopkins Precursors Study. Arch Intern Med 1999;159:957–963.

    In this observational longitudinal study of former medical students, being overweight at the age of 25 predicted the development of diabetes.

26. (1) **Bosch J** et al. Effect of ramipril on the incidence of diabetes. N Engl J Med 2006;355(15):1551–1562.

    In this double-blind, randomized clinical trial, 5,269 participants without cardiovascular disease but with impaired fasting glucose levels or impaired glucose tolerance were given ramipril or

placebo and were followed for a median of 3 years. Participants receiving ramipril were more likely to have regression to normoglycemia than those receiving placebo (hazard ratio, 1.16; 95% CI, 1.07 to 1.27; $p = 0.001$). At the end of the study, the median fasting plasma glucose level was not significantly lower in the ramipril group (102.7 mg/dl [5.70 mmol/l]) than in the placebo group (103.4 mg/dl [5.74 mmol/l], $p = 0.07$); however, plasma glucose levels 2 hours after an oral glucose load were significantly lower in the ramipril group (135.1 mg/dl [7.50 mmol/l] vs. 140.5 mg/dl [7.80 mmol/l], $p = 0.01$).

Treatment

27. (1) **Knowler WC** et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393–403.

Lifestyle intervention and metformin reduced the incidence of type 2 DM in patients with elevated fasting glucose measurements (but not determined to have diabetes). Lifestyle changes were more effective than in findings related to metformin.

28. (1) **UK Prospective Diabetes Study Group (UKPDS 7)**. Response of fasting plasma glucose to diet therapy in newly presenting type II patients with diabetes. Metabolism 1990;39:905–912.

This randomized multicenter clinical trial studied the effects of variable interventions on multiple clinical outcomes, including diabetic complications, in newly diagnosed type 2 DM patients in the United Kingdom. The results of 3,044 patients treated with dietary intervention were studied; other UKPDS reports studied varying numbers of patients. A considerable variation was noted in the response to diet in patients with newly diagnosed type 2 DM. Patients with higher glucose concentrations and those who lost more weight responded by greater declines in glucose concentrations. Weight loss of 28% of ideal body weight was required to achieve near-normal glycemia in patients whose fasting plasma glucose levels exceeded 180 mg/dl. Fasting plasma glucose response to diet is determined more by caloric restrictions than by weight loss.

29. (1) **Lindström J** et al. Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: Follow-up of the Finnish Diabetes Prevention Study. The Lancet 2006;368(9548):1673–1679.

In this study, overweight, middle-aged men ($n = 172$) and women ($n = 350$) with impaired glucose tolerance were randomly assigned to intensive lifestyle intervention or control group. After a median of 4 years of active intervention period, participants who were still free of diabetes were further followed up for a median of 3 years, with median total follow-up of 7 years. During the total follow-up, the incidence of type 2 diabetes was 4.3 and 7.4 per 100 person-years in the intervention and control group, respectively (log-rank test $p = 0.0001$), indicating 43% reduction in relative risk. The risk reduction was related to the success in achieving the intervention goals of weight loss, reduced intake of total and saturated fat and increased intake of dietary fiber, and increased physical activity. Beneficial lifestyle changes achieved by participants in the intervention group were maintained after the discontinuation of the intervention, and the corresponding incidence rates during the postintervention follow-up were 4.6 and 7.2 ($p = 0.0401$), indicating 36% reduction in relative risk.

30. (2) **UK Prospective Diabetes Study Group (UKPDS 34).** Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes. Lancet 1998;352:854–865.

The use of metformin in overweight patients with type 2 DM reduced mortality, stroke, and diabetes complications, suggesting that metformin is the drug of choice in patients with type 2 DM who are overweight. It is not associated with serious hypoglycemic side effects.

31. (1) **Johansen K**. Efficacy of metformin in the treatment of NIDDM: Meta-analysis. Diabetes Care 1999;22:33–37.

This was a meta-analysis of nine randomized controlled trials comparing metformin with placebo and 10 trials comparing metformin with sulfonylurea. Sulfonylurea and metformin had similar effects on lowering glucose and glycated hemoglobin. Sulfonylurea caused weight gain of 1.7 kg on an average, whereas metformin was associated with a weight loss of 1.2 kg.

32. (1) **Fanghanel G** et al. Metformin's effects on glucose and lipid metabolism in patients with secondary failure to sulfonylureas. Diabetes Care 1996;19:1185–1189.

In a small randomized controlled trial, the effectiveness of metformin and insulin was compared in patients considered to have been failed by sulfonylurea therapy. Metformin effectively reduced hemoglobin A_{1c} from 12.8% to 8.9%, triglycerides, cholesterol, and BMI. Insulin treatment was also effective but did not influence BMI, cholesterol, or hypertension.

33. (1) **UK Prospective Diabetes Study Group (UKPDS 13).** Relative efficacy of randomly allocated diet, sulphonylurea, insulin, or metformin in patients with newly diagnosed non-insulin dependent diabetes followed for three years. BMJ 1995;310:83–88.

Sulfonylurea, insulin, and metformin controlled glucose levels effectively in patients with newly diagnosed type 2 DM in a similar fashion and were superior to diet alone. Sulfonylurea and insulin were associated with weight gain of 3.5 to 4.8 kg over a 3-year period, whereas metformin was not associated with significant weight changes.

34. (1) **UK Prospective Diabetes Study Group (UKPDS 28).** A randomized trial of efficacy of early addition of metformin in sulfonylurea-treated type 2 diabetes. Diabetes Care 1998;21:87–92.

    Adding metformin to the pharmacotherapeutic regimen of 591 subjects taking sulfonylurea reduced glucose effectively and reduced the rates of "marked hyperglycemia" development when compared with findings in patients receiving sulfonylurea as monotherapy.

35. (1) **Blohme G** et al. Glibenclamide and glipizide in maturity-onset diabetes: A double-blind cross-over study. Acta Med Scand 1979;206:263–267.

    Sulfonylureas have similar clinical effects on lowering blood glucose.

36. (1) **UK Prospective Diabetes Study Group (UKPDS 33)**. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. Lancet 1998;352:837–853.

    This is another publication from the UKPDS group of 3,867 patients with newly diagnosed type 2 DM. Patients were randomly assigned to the intensive arm of the study (i.e., insulin treatment or sulfonylureas, chlorpropamide, glibenclamide, or glipizide) or the conventional arm with diet. Subjects in the intensive group had a higher number of hypoglycemic episodes than did those in the conventional group ($p < 0.0001$). Major hypoglycemic episode rates were 0.7% with conventional treatment, 1.0% with chlorpropamide, 1.4% with glibenclamide, and 1.8% with insulin per year, respectively. Weight gain was higher in the intensive group (2.9 kg) than in the conventional group ($p < 0.001$). Finally, subjects who took insulin had a greater weight gain (4.0 kg) than those assigned chlorpropamide (2.6 kg) or glibenclamide (1.7 kg). In sum, sulfonylurea and insulin intensive therapy reduced microvascular diabetic complications but not macrovascular disease.

37. (2) **Matthews DR** et al. for the UK Prospective Diabetes Study Group (UKPDS 26). Sulphonylurea failure in non-insulin-dependent patients with diabetes over six years. Diabet Med 1998;15:297–303.

    In 1,305 patients newly diagnosed with type 2 DM and started on sulfonylurea, 48% required additional treatment by 6 years, especially patients whose BMI was less than 30 kg/m^2.

38. (1) **Rosenstock J** et al. Glimepiride, a new once-daily sulfonylurea: A double-blind placebo-controlled study of NIDDM patients: Glimepiride Study Group. Diabetes Care 1996;19:1194–1199.

    Patients with type 2 DM were assigned to glimepiride (8–16 mg) or placebo. Hemoglobin A_{1c} increased from 7.7% to 9.7% in the placebo group but decreased from 7.9% to 8.1% with glimepiride.

39. (1) **Chiasson JL** et al. The efficacy of acarbose in the treatment of patients with non-insulin-dependent diabetes mellitus: A multicenter controlled clinical trial. Ann Intern Med 1994;121:928–935.

    Acarbose treatment improved glycemic control in type 2 DM patients who took acarbose monotherapy or in combination with metformin, sulfonylurea, or insulin.

40. (1) **Holman RR** et al. for the UK Prospective Diabetes Study Group (UKPDS 44). A randomized double-blind trial of acarbose in type 2 diabetes shows improved glycemic control over 3 years. Diabetes Care 1999;22:960–964.

    When compared with placebo, acarbose monotherapy or combination therapy reduced hemoglobin A_{1c} by 0.2% to 0.5% in patients with type 2 DM over a period of 3 years. Noncompliance with therapy was mainly due to side effects of flatulence and diarrhea.

41. (1) **Wolffenbuttel BH, Landgraf R**. A 1-year multicenter randomized double-blind comparison of repaglinide and glyburide for the treatment of type 2 diabetes: Dutch and German Repaglinide Study Group. Diabetes Care 1999;22:463–467.

    Repaglinide's action is similar to that of glyburide in reducing plasma glucose concentrations; adverse effect profile also is similar.

42. (1) **Nissen SE** et al. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med, 2007;356(24):2457–2471.

    Data from 42 trials and registries on subjects using rosiglitazone and their controls were combined for this study. The mean age of the subjects was approximately 56 years, and the mean baseline glycated hemoglobin level was approximately 8.2%. In the rosiglitazone group, as compared with the control group, the odds ratio for MI was 1.43 (95% confidence interval [CI], 1.03 to 1.98; $p = 0.03$), and the odds ratio for death from cardiovascular causes was 1.64 (95% CI, 0.98 to 2.74; $p = 0.06$).

43. (3) **Dore DD** et al. Use of a claims-based active drug safety surveillance system to assess the risk of acute pancreatitis with exenatide or sitagliptin compared to metformin or glyburide. Curr Med Res Opin 2009;25(4):1019–1027.

The study population was derived from a large US commercial health insurance transaction database. Data were obtained from June 2005 through June 2008. Cohorts of exenatide and sitagliptin were each matched to an equal number of metformin or glyburide (met/gly) users. The results indicated that during follow-up of up to 1 year, acute pancreatitis occurred among 0.13% of patients treated with exenatide and 0.12% of patients treated with sitagliptin. The risk of acute pancreatitis was comparable for initiators of exenatide (RR 1.0; 95% CI 0.6–1.7) and sitagliptin (RR 1.0; 95% CI 0.5–2.0) relative to the comparison cohorts, suggesting that no evidence for an association of acute pancreatitis among initiators of exenatide or sitagliptin compared to metformin/glyburide initiators.

44. (1) **Buse JB** et al. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes. Diabetes Care 2004;27(11):2628–2635.

In this blind, placebo-controlled, short-duration study (30 weeks), 377 subjects on sulfonylurea therapy were randomized (60% men, age 55 +/− 11 years, BMI 33 +/− 6 kg/m^2, HbA(1c) 8.6 +/− 1.2% [+/−SD]) and began 4 weeks at 5 μg subcutaneous exenatide twice daily or placebo. Subsequently, a subgroup of subjects was escalated to 10 μg b.i.d. of exenatide. At week 30, HbA(1c) changes from baseline were −0.86 +/− 0.11, −0.46 +/− 0.12, and 0.12 +/− 0.09% (+/−SE) in the 10-μg, 5-μg, and placebo arms, respectively (adjusted $p < 0.001$), indicating that exenatide significantly reduced HbA(1c) in patients with type 2 diabetes, failing maximally effective doses of a sulfonylurea.

45. (1) **Buse JB** et al. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: A 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). Lancet 2009;374(9683):39–47.

In this study, adults with inadequately controlled type 2 diabetes on maximally tolerated doses of metformin, sulfonylurea, or both were stratified to receive additional liraglutide 1.8 mg once a day ($n = 233$) or exenatide 10 μg twice a day ($n = 231$) in a 26-week open-label, parallel-group study. The primary outcome was change in glycosylated hemoglobin (HbA[1c]). Efficacy analyses were by intention to treat. Results indicated that the mean baseline HbA(1c) for the study population was 8.2%. Liraglutide reduced mean HbA(1c) significantly more than did exenatide (−1.12% [SE 0.08] vs. −0.79% [0.08]; estimated treatment difference −0.33; 95% CI −0.47 to −0.18; $p < 0.0001$), and more patients achieved a HbA(1c) value of less than 7% (54% vs. 43%, respectively; odds ratio 2.02; 95% CI 1.31 to 3.11; $p = 0.0015$). Liraglutide reduced mean fasting plasma glucose more than did exenatide ($p < 0.0001$), but postprandial glucose control was less effective after breakfast and dinner. Both drugs promoted similar weight losses (liraglutide −3.24 kg vs. exenatide −2.87 kg).

Diabetic Ketoacidosis

Etiology, Epidemiology, and Presentation

46. (3) **Rewers A** et al. Predictors of acute complications in children with type 1 diabetes. JAMA 2002;287:2511–2518.

In this cohort of 1,243 children with type 1 DM who lived in Denver, Colorado, incidence of ketoacidosis was 8 per 100 person-years. In multivariate analysis, the risk for ketoacidosis increased with higher hemoglobin A_{1c} and higher dose of insulin use in older children. Other factors played an important role, such as under insurance coverage and the concurrent presence of psychiatric disorders.

47. (2) **Johnson DD** et al. Diabetic ketoacidosis in a community-based population. Mayo Clin Proc 1980;55:83–88.

In this community-based case-matched retrospective review of 92 patients with DKA, infection was the main precipitating factor for the episodes.

48. (2) **Faich GA** et al. The epidemiology of diabetic acidosis: A population-based study. Am J Epidemiol 1983;117:551–558.

The presentation of and precipitating factors for 137 patients with DKA are discussed. Twenty percent of patients were those with newly developed diabetes.

49. (2) **Malone ML** et al. Characteristics of diabetic ketoacidosis in older versus younger adults. J Am Geriatr Soc 1992;40:1100–1104.

This was a retrospective chart review of 220 cases of DKA. Twenty-seven cases occurred in patients who were older than 65 years. Treatment of DKA in this age group was associated with increased hypoglycemia and higher rates of death.

Treatment

50. (1) **Fisher JN** et al. Diabetic ketoacidosis: Low-dose insulin therapy by various routes. N Engl J Med 1977;297:238–247.

In this randomized controlled study of 45 patients with DKA, three groups receiving insulin therapy by various routes were compared. When compared with the groups receiving subcutaneous or intramuscular insulin, the group receiving low-dose intravenous insulin had a faster rate of fall of plasma glucose ($p = 0.01$) but no significant change in time to recovery. This route was also more effective initially in reducing ketone levels ($p < 0.05$).

51. (1) **Burghen GA** et al. Comparison of high-dose and low-dose insulin by continuous intravenous infusion in the treatment of diabetic ketoacidosis in children. Diabetes Care 1980;3:15–20.

In this randomized controlled study, low-dose intravenous insulin was compared with high-dose intravenous insulin (0.1 vs. 1 U/kg/hr) in 32 patients with DKA. Low-dose insulin resulted in slower rates of glucose decline but was as effective as high-dose insulin in treating DKA and recovery. Furthermore, a lower incidence of significant hypoglycemia was found in patients receiving low-dose insulin.

52. (2) **Carroll P, Matz R**. Uncontrolled diabetes mellitus in adults: Experience in treating diabetic ketoacidosis and hyperosmolar coma with low-dose insulin and uniform treatment regimen. Diabetes Care 1983;6:579–585.

Retrospective analysis of 275 patients with uncontrolled diabetes who received low-dose insulin regimens and fluid resuscitation with hypotonic solutions, leading to a lower mortality rate than expected. DKA mortality increased in those who were older than 50 years.

53. (1) **Edwards GA** et al. Effectiveness of low-dose continuous intravenous insulin infusion in diabetic ketoacidosis: A prospective comparative study. J Pediatr 1977;91:701–705.

In this randomized controlled study of 20 pediatric patients, low-dose insulin intravenously was compared with high-dose insulin subcutaneously. No statistical difference was observed in the rate of correction of DKA or reduction of plasma glucose measurements.

54. (2) **Lever E, Jaspan JB**. Sodium bicarbonate therapy in severe diabetic ketoacidosis. Am J Med 1983;75:263–268.

In this retrospective analysis of 95 cases of DKA, the authors found no difference between patients who received bicarbonate therapy (72 cases) and those who did not (22 cases).

55. (1) **Morris LR** et al. Bicarbonate therapy in severe diabetic ketoacidosis. Ann Intern Med 1986;105:836–840.

In this randomized controlled trial, 10 patients with DKA were treated with bicarbonate and 11 were not. No significant difference was seen in outcome or benefits.

56. (2) **Glaser N** et al. Risk factors for cerebral edema in children with diabetic ketoacidosis: The Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics. N Engl J Med 2001;344:264–269.

In this case-matched report of 61 children with DKA, cerebral edema was associated with lower partial pressures of arterial carbon dioxide and higher levels of serum urea nitrogen. Treatment with bicarbonate was associated with increased rates of cerebral edema.

57. (1) **Fisher JN, Kitabchi AE**. A randomized study of phosphate therapy in the treatment of diabetic ketoacidosis. J Clin Endocrinol Metab 1983;57:177–180.

In this randomized controlled study, 15 patients with DKA received phosphate treatment and were compared with another 15 patients who did not receive phosphate treatment. No statistical difference was found in serum electrolytes, 2,3-DPG levels, or recovery from DKA. Phosphate treatment resulted in hypocalcemia.

58. (3) **Rosenbloom AL**. Intracerebral crises during treatment of diabetic ketoacidosis. Diabetes Care 1990;13:22–33.

In this report of 69 cases of intracerebral complications after DKA, most of the patients were children younger than 5 years. Pathologic findings varied and included localized brain edema, hemorrhage, thrombosis, and infection.

59. (3) **Krane EJ** et al. Subclinical brain swelling in children during treatment of diabetic ketoacidosis. N Engl J Med 1985;312:1147–1151.

Computed tomography scans from six children who received treatment for DKA showed evidence of subclinical brain swelling during therapy.

Hyperosmolar Coma

60. (2) **Wachtel TJ** et al. Predisposing factors for the diabetic hyperosmolar state. Arch Intern Med 1987;147:499–501.

In this case-controlled study of 135 patients with hyperosmolar coma who were matched to randomly selected patients with diabetes, predictors of the development of hyperosmolar coma were female gender, newly diagnosed diabetes, and acute infection.

61. (2) **Gale EA** et al. Severely uncontrolled diabetes in the over-fifties. Diabetologia 1981;21:25–28.

In this observational study of 317 patients admitted to hospital with severely uncontrolled diabetes and hyperglycemia, 43% of patients older than 50 years died as a result. About 30% of patients had not previously been diagnosed with diabetes.

62. (2) **Khardori R, Soler NG**. Hyperosmolar hyperglycemic nonketotic syndrome: Report of 22 cases and brief review. Am J Med 1984;77:899–904.

In this observational study of 22 patients with hyperosmolar coma, the mortality rate was 36%.

63. (2) **Wachtel TJ** et al. Hyperosmolarity and acidosis in diabetes mellitus: A three-year experience in Rhode Island. J Gen Intern Med 1991;6:495–502.

This retrospective chart review study described features of 278 subjects in Rhode Island who were diagnosed with hyperosmolar coma over a 3-year period. Infection was the most frequent precipitating factor (27%). Mortality rates were 12%, and mortality was associated with older age, higher osmolality, and residing in a nursing home.

64. (2) **Fulop M** et al. Hyperosmolar nature of diabetic coma. Diabetes 1975;24:594–599.

In this observational study of 47 patients with hyperosmolar coma, obtundation and impaired consciousness were related to the severity of hyperglycemia regardless of the degree of ketoacidosis.

Treatment

65. (2) **Keller U** et al. Course and prognosis of 86 episodes of diabetic coma: A five year experience with a uniform schedule of treatment. Diabetologia 1975;11:93–100.

In this small descriptive study, 58 episodes of severe diabetic ketoacidotic coma and of 28 episodes of nonketotic coma (total 86) are compared. The nonketotic patients were older. A comparison of the age groups of survivors and those patients who died within 72 hours showed an increase in mortality with age. On admission, blood glucose, osmolarity, and blood urea were higher in the fatal cases. Blood urea was the most important indicator of a fatal outcome. The response of blood glucose to insulin was impaired in the subsequently fatal cases. Early mortality was 14% in the ketotic and 29% in the nonketotic cases. The most frequent causes of death were circulatory failure.

66. (2) **To LB, Phillips PJ**. Hyperosmolar non-ketotic diabetic coma: Less sodium in therapy? Anaesth Intensive Care 1980;8:349–352.

Retrospective observational study of 18 patients with hyperosmolar coma showing elevated serum sodium concentration with standard therapy. The use of dextrose infusion is recommended to avoid electrolyte abnormalities.

67. (2) **Rosenthal NR, Barrett EJ**. An assessment of insulin action in hyperosmolar hyperglycemic nonketotic patients with diabetes. J Clin Endocrinol Metab 1985;60:607–610.

In this experimental study, rates of glucose decline after administration of insulin and fluids were less than those in nondiabetic subjects, suggesting a state of insulin resistance in hyperosmolar coma.

68. (2) **Bendezu R** et al. Experience with low-dose insulin infusion in diabetic ketoacidosis and diabetic hyperosmolarity. Arch Intern Med 1978;138:60–62.

In this comparative observational study, low-dose insulin injections resulted in a satisfactory decrease of serum glucose in patients with hyperosmolar coma as well as DKA. Patients with hyperosmolar coma were more sensitive to insulin than were DKA patients.

Hypoglycemia

Etiology and Diagnosis

69. (1) **Brunelle BL** et al. Meta-analysis of the effect of insulin Lispro on severe hypoglycemia in patients with type 1 diabetes. Diabetes Care 1998;21:1726–1731.

In this meta-analysis of eight trials, 2,576 patients with type 1 DM were included. Insulin lispro treatment was associated with less severe hypoglycemia than was that with regular insulin (3.1% vs. 4.4% of patients) and (102 vs. 131 episodes; $p = 0.024$).

70. (1) **Home PD** et al. Insulin Aspart vs. human insulin in the management of long-term blood glucose control in type 1 diabetes: A randomized controlled trial. Diabetes Med 2000;17:762–770.

In this multicenter randomized open-label study, 1,070 patients were randomly assigned to receive the insulin Aspart or human insulin. Insulin Aspart improved levels of glycated hemoglobin and postprandial glucose but not preprandial glucose levels. Insulin Aspart treatment was associated with less severe nocturnal hypoglycemia (1.3% vs. 3.4%; $p < 0.05$) as well as less hypoglycemia after a meal (1.8% vs. 5%; $p < 0.005$).

71. (1) **MacLeod KM** et al. A comparative study of responses to acute hypoglycemia induced by human and porcine insulins in patients with type 1 diabetes. Diabet Med 1996;13:346–357.

In a double-blind crossover trial, the effects of insulin ("human engineered" vs. animal derived)-induced hypoglycemia on physiologic as well as counterregulatory hormonal responses were compared in 40 patients with type 1 DM. The magnitude and pattern of response of counter-regulatory hormones to hypoglycemia induced by either of these insulins were indistinguishable, as were the scores of autonomic and neural glycopenic symptoms.

72. (2) **Fischer KF** et al. Hypoglycemia in hospitalized patients: Causes and outcomes. N Engl J Med 1986;315:1245–1250.

Unblinded retrospective cohort study of 94 hospital patients. The predictors of hypoglycemia were missing meals, renal and hepatic disease, infections, shock, burns, cancer, and pregnancy.

73. (3) **Feher MD** et al. Hypoglycaemia in an inner-city accident and emergency department: A 12-month survey. Arch Emerg Med 1989;6:183–188.

A missed meal accounted for 52% of all precipitating causes of hypoglycemia in a 12-month survey in this inner-city emergency department practice report.

74. (2) **Muhlauser I** et al. Risk factors of severe hypoglycemia in adult patients with type I diabetes: A prospective population-based study. Diabetologia 1998;41:1274–1282.

This was a prospective observational study of 669 patients with type 1 DM and hypoglycemia. Predictors of hypoglycemia were prior severe hypoglycemia (HR, 1.9), goal of glycemic control (HR, 0.07), and impaired awareness, among other factors.

75. (2) **Davis EA** et al. Hypoglycemia: Incidence and clinical predictors in a large population-based sample of children and adolescents with IDDM. Diabetes Care 1997;20:22–25.

In this observational trial, rates of hypoglycemia were higher in children younger than 6 years and were higher in those who had tight glucose control (hemoglobin $A_{1c} < 7\%$; $p < 0.001$).

76. (2) **Gold AE** et al. Frequency of severe hypoglycemia in patients with type 1 diabetes with impaired awareness of hypoglycemia. Diabetes Care 1994;17:697–703.

In this small prospective comparative trial, 29 patients with type 1 DM who had impaired awareness were compared with 31 type 1 DM patients with intact awareness. Sixty-six percent of patients with such awareness had severe hypoglycemia compared with 26% of patients from the other group ($p < 0.01$).

77. (2) **Stephenson JM** et al. Is autonomic neuropathy a risk factor for severe hypoglycemia? The EURO-DIAB IDDM Complications Study. Diabetologia 1996;39:1372–1376.

In this European study of more than 3,000 patients with diabetes, combined autonomic deficit in heart rate and blood pressure responses to standing were associated with a modest increase in the risk of severe hypoglycemia.

78. (2) **Diabetes Control and Complications Trial Research Group**. Hypoglycemia in the Diabetes Control and Complications Trial. Diabetes 1997;46:271–286.

In this DCCT study, there were 3,788 episodes of severe hypoglycemia, and 1,027 of these episodes resulted in seizures or coma. The relative risk for coma or seizure was 3.0 for intensive therapy. This increased risk persisted for each year during the follow-up period of 9 years. Intensive treatment was also associated with an increased risk of multiple episodes within the same patient. Within each treatment group (intensive vs. conventional), the number of previous episodes of hypoglycemia was a good predictor of risk of future episode and so was the current glycated hemoglobin level.

79. (1) **Diabetes Control and Complications Trial Research Group**. Effect of intensive diabetes treatment on the development and progression of long-term complications in adolescents with insulin-dependent diabetes mellitus. J Pediatr 1994;125:177–188.

This analysis from the DCCT group focused on 195 patients with type 1 DM between the ages of 13 to 17 years. In this report, a threefold increase of severe hypoglycemia was found in the intensively treated group.

80. (2) **Berger W** et al. The relatively frequent incidence of severe sulfonylurea-induced hypoglycemia in the last 25 years in Switzerland: Results of 2 surveys in Switzerland in 1969 and 1984. Schweiz Med Wochenschr 1986;116:145–151.

In this observational study, the incidence of oral agent–induced hypoglycemia was 0.22 to 0.24 per 1,000 patients. Use of chlorpropamide or glibenclamide was associated with higher frequency of hypoglycemia than was use of tolbutamide.

81. (1) **Landgraf R** et al. A comparison of repaglinide and glibenclamide in the treatment of type 2 patients with diabetes previously treated with sulphonylureas. Eur J Clin Pharmacol 1999;55:165–171.

In this randomized controlled study of 195 patients with type 2 DM, no significant difference in adverse events including hypoglycemia was seen between the groups using repaglinide and glibenclamide.

Treatment

82. (2) **Slama G** et al. The search for an optimized treatment of hypoglycemia: Carbohydrates in tablets, solution, or gel for the correction of insulin reactions. Arch Intern Med 1990;150:589–593.

In this French study, hypoglycemia was induced in 41 patients with type 1 DM. Blood glucose concentrations at 10 minutes were similar for glucose, sucrose, or polysaccharide treatment. Treatment with glucose tablets did not produce results that differed from those found with glucose solution. Fruit juice and glucose gel did not raise glucose levels effectively at 10 minutes.

83. (2) **Wiethop BV, Cryer PE**. Alanine and terbutaline in treatment of hypoglycemia in IDDM. Diabetes Care 1993;16:1131–1136.

In this study, oral glucose and subcutaneous glucagon increased plasma glucose concentrations in hypoglycemic type 1 DM patients quickly over 30- to 60-minute periods, but this glucose increase was transient. Glucose levels increased to nearly 11 mmol/l.

84. (2) **Palatnick W** et al. Clinical spectrum of sulfonylurea overdose and experience with diazoxide therapy. Arch Intern Med 1991;151:1859–1862.

This was a retrospective study of 40 episodes of oral agent–induced hypoglycemia. Six patients had severe, resistant hypoglycemia that responded to intravenous diazoxide.

85. (2) **Fanelli CS** et al. Long-term recovery from unawareness, deficient counterregulation, and lack of cognitive dysfunction during hypoglycemia, following institution of rational, intensive insulin therapy in IDDM. Diabetologia 1994;37:1265–1276.

In this study, glycemic goals were relaxed in 21 patients with type 1 DM with hypoglycemia unawareness. This action resulted in an increase of hemoglobin A_{1c} by 1% over 1 year and reduced the frequency of hypoglycemia significantly.

86. (2) **Northam EA** et al. Neuropsychological profiles of children with type 1 diabetes 6 years after disease onset. Diabetes Care 2001;24:1541–1546.

In this Australian study, patients with type 1 DM were followed up prospectively after the onset of disease. Neuropsychological tests were performed at 2 and 6 years after diagnosis. The results of a 6-year follow-up of 90 patients with diabetes indicated that the neuropsychological profiles are affected by severe hypoglycemia, particularly in very young children.

87. (2) **Detlofson I** et al. Oral bedtime cornstarch supplementation reduces the risk for nocturnal hypoglycaemia in young children with type 1 diabetes. Acta Paediatr 1999;88:595–597.

In this randomized controlled study, bedtime snacks reduced episodes of hypoglycemia by 64% in 14 preschool children.

Complications of Diabetes

Cardiovascular Disease

88. (2) **Stamler J** et al. Diabetes, other risk factors, and 12-year cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. Diabetes Care 1993;16:434–444.

In this observational study, 12% of 5,163 men who took diabetes medications died of cardiovascular disease over a period of 12 years compared with 6% of men who did not take diabetic medications.

89. (2) **Stratton IM** et al. (UKPDS 35). Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes: Prospective observational study. BMJ 2000;321:405–412.

In this report from UKPDS, hemoglobin A_{1c} reduction by 1% led to a reduction of 14% for MI.

90. (2) **Agewall S** et al. Usefulness of microalbuminuria in predicting cardiovascular mortality in treated hypertensive men with and without diabetes mellitus: Risk Factor Intervention Study Group. Am J Cardiol 1997;80:164–169.

In this small study, microalbuminuria predicted cardiovascular disease in patients with diabetes.

91. (1) **Cushman WC** et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med. 362(17):1575–1585.

In this study, a total of 4,733 participants with type 2 diabetes were randomly assigned to intensive therapy, targeting a systolic pressure of less than 120 mm Hg, or standard therapy, targeting a systolic pressure of less than 140 mm Hg. The primary composite outcome was nonfatal MI, nonfatal stroke, or death from cardiovascular causes. The mean follow-up was 4.7 years.

After 1 year, the mean systolic blood pressure was 119.3 mm Hg in the intensive-therapy group and 133.5 mm Hg in the standard-therapy group. The annual rate of the primary outcome was 1.87% in the intensive-therapy group and 2.09% in the standard-therapy group (hazard ratio with intensive therapy, 0.88; 95% CI, 0.73 to 1.06; $p = 0.20$). The annual rates of death from any cause were 1.28% and 1.19% in the two groups, respectively (hazard ratio, 1.07; 95% CI, 0.85 to 1.35; $p = 0.55$). The annual rates of stroke were 0.32% and 0.53% in the two groups, respectively (hazard ratio, 0.59; 95% CI, 0.39 to 0.89; $p = 0.01$). As such, this study concludes that in patients with type 2 diabetes at high risk for cardiovascular events, targeting a systolic blood pressure of less than 120 mm Hg as compared with less than 140 mm Hg, did not reduce the rate of a composite outcome of fatal and nonfatal major cardiovascular events.

92. (1) **Lindholm LH** et al. Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention for Endpoint Reduction in Hypertension Study (LIFE): A randomised trial against atenolol: The LIFE Study Group. Lancet 2002;359:1004–1010.

In this study, 1,195 patients with diabetes and hypertension were randomly assigned to receive atenolol or losartan. Mortality from all causes and mortality from cardiovascular disease were significantly lower in the losartan group, by 61% and 63%, respectively.

93. (1) **Heart Outcomes Prevention Evaluation (HOPE) Study Investigators**. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: Results of the HOPE study and MICRO-HOPE substudy. Lancet 2000;355:253–259.

In this randomized study, 3,577 patients with diabetes with or without preexisting cardiovascular disease were assigned to ramipril, 10 mg/d. After 4.5 years of follow-up, ramipril lowered the risk of MI by 22%, stroke by 33%, overt nephropathy by 24%, and cardiovascular death by 37%.

94. (2) **Pyorala K** et al. Cholesterol lowering with simvastatin improves prognosis of patients with diabetes with coronary heart disease: A subgroup analysis of the Scandinavian Simvastatin Survival Study (4S). Diabetes Care 1997;20:614–620.

In this subgroup analysis of the 4S study, 202 patients with diabetes and hypercholesterolemia were randomly assigned to simvastatin treatment, which reduced cardiovascular events.

95. (2) **Rubins HB** et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. N Engl J Med 1999;341:410–418.

In this study, 627 men with diabetes and 1,904 men without diabetes were randomly assigned to gemfibrozil or placebo. After 5.1 years of follow-up, a relative reduction of 24% was noted in the combined incidence of stroke, cardiovascular death, and nonfatal MI.

96. (1) **Goldberg RB** et al. Cardiovascular events and their reduction with pravastatin in diabetic and glucose-intolerant myocardial infarction survivors with average cholesterol levels: Subgroup analyses in the Cholesterol and Recurrent Events (CARE) Trial: The CARE Investigators. Circulation 1998;98:2513–2519.

In this subgroup analysis of the CARE trial, 586 patients with diabetes were randomly assigned to pravastatin or placebo. The group using pravastatin reduced the absolute risk of cardiovascular event by 8%.

97. (1) **Malmberg K** et al. Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in patients with diabetes with acute myocardial infarction (DIGAMI study): Effects on mortality at 1 year. J Am Coll Cardiol 1995;26:57–65.

In this randomized controlled study, 620 patients were randomly assigned to receive insulin infusion followed by subcutaneous insulin for a period of 3 months or conventional diabetes treatment soon after diagnosis of acute MI. The relative mortality rate was reduced by 29% in the group using insulin infusion at 1 year.

98. (1) **Bypass Angioplasty Revascularization Investigation (BARI) Investigators**. Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease. N Engl J Med 1996;335:217–225.

Among patients with diabetes and multivessel cardiac disease, revascularization with coronary artery bypass graft had a better 5-year survival rate than did angioplasty (80.6% vs. 65.5%; $p = 0.003$).

Eye Disease

99. (1) **Chaturvedi N** et al. Effect of lisinopril on progression of retinopathy in normotensive people with type 1 diabetes. Lancet 1998;351:28–31.

    In this randomized controlled study, 220 patients with type 1 DM and retinopathy were randomly assigned to receive lisinopril versus placebo and observed during 2 years of follow-up. Lisinopril use was associated with a 50% reduction of progression of retinopathy.

100. (1) **Chew EY** et al. Effects of aspirin on vitreous/preretinal hemorrhage in patients with diabetes mellitus: ETDRS Report no. 20. Arch Ophthalmol 1995;113:52–55.

    The ETDRS was a randomized controlled study designed to assess the benefit of laser panretinal photocoagulation in reducing severe visual loss in 3,711 patients with nonproliferative or mild proliferative diabetic retinopathy. During intervention, patients were randomly assigned to receive aspirin, 650 mg/d, or placebo. In addition, one eye was assigned to early treatment with photocoagulation, and the other eye served as control in each patient. Results showed that vitreous or preretinal hemorrhage occurred in 39% of eyes assigned to aspirin and 37% assigned to placebo ($p = 0.3$). The conclusion was that aspirin therapy caused no harm.

101. (1) **Early Treatment Diabetic Retinopathy Study Research Group**. Early photocoagulation for diabetic retinopathy: ETDRS Report no. 9. Ophthalmology 1991;98(suppl):766–785.

    This is another report from the ETDRS demonstrating that focal photocoagulation is effective in macular edema.

102. (1) **Diabetic Retinopathy Study.** Photocoagulation treatment of proliferative diabetic retinopathy: The second report of Diabetic Retinopathy Study findings. Ophthalmology 1978;85:82–106.

    The DRS was a randomized controlled study of laser (xenon and argon) panretinal photocoagulation in the prevention of severe visual loss. This study provided evidence of benefit for laser treatment in patients with diabetic proliferative retinopathy.

103. (2) **Ferris F.** Early photocoagulation in patients with either type I or type II diabetes. Trans Am Ophthalmol Soc 1996;94:505–537.

    In this analysis of the ETDRS, patients with type 2 DM and older patients with diabetes benefited from scatter photocoagulation if they were diagnosed with severe nonproliferative retinopathy or early proliferative retinopathy.

104. (2) **Kohner EM** et al. (UKPDS 52). Relationship between the severity of retinopathy and progression to photocoagulation in patients with type 2 DM in the UKPDS. Diabetes Med 2001;18:178–184.

    Another report from the UKPDS demonstrating that few patients with type 2 DM without retinopathy would progress to significant retinopathy requiring photocoagulation after 3 to 6 years of follow-up

Diabetic Neuropathy

105. (2) **Dyck PJ** et al. The prevalence by staged severity of various types of diabetic neuropathy, retinopathy, and nephropathy in a population-based cohort: The Rochester Diabetic Neuropathy Study. Neurology 1993;43:817–824.

    The prevalence of neuropathy in 380 patients with type 1 and type 2 DM residing in Rochester, Minnesota, was examined in this study.

106. (2) **Dyck PJ** et al. The Rochester Diabetic Neuropathy Study: Reassessment of tests and criteria for diagnosis and staged severity. Neurology 1992;42:1164–1170.

    In this report of the Rochester Diabetic Neuropathy Study, nerve conduction and quantitative autonomic testing were found to be most sensitive and objective in detection of neuropathy.

107. (1) **Nicolucci A** et al. A meta-analysis of trials on aldose reductase inhibitors in diabetic peripheral neuropathy: The Italian Study Group: The St. Vincent Declaration. Diabetes Med 1996;13:1017–1026.

    In this meta-analysis of 13 randomized clinical trials comparing the effects of aldose reductase inhibitors with placebo, as measured by nerve conduction studies, a significant reduction in decline was noted for the median nerve motor velocities but not peroneal motor, median sensory, or sural sensory velocities. Other results, benefits, and adverse effects were unclear.

108. (2) **Argoff CE** et al. Consensus Guidelines: Treatment planning and options. Mayo Clin Proc 2006;81(4 suppl):S12–S25.

    In this review of clinical trials, the authors divide medical treatment of painful diabetic neuropathy to first-tier and second-tier treatments.

109. (1) **Backonja M** et al. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: A randomized controlled trial. JAMA 1998;280:1831–1836.

In this randomized controlled study, 165 patients were assigned to gabapentin or placebo. The use of gabapentin reduced daily pain scores more than did placebo.

110. (1) **Zhang WY** et al. The effectiveness of topically applied capsaicin: A meta-analysis. Eur J Clin Pharmacol 1994;46:517–522.

In this meta-analysis, capsaicin was better than placebo in treating diabetic neuropathy (OR, 2.74; CI, 1.73–4.3).

Renal Disease

111. (1) **Warram J** et al. Progression of microalbuminuria to proteinuria in type 1 diabetes: Nonlinear relationship with hyperglycemia. Diabetes 2000;49:94–100.

In this study, 279 type 1 DM patients with microalbuminuria were observed for a period of 4 years. The rate of progression increased steeply at levels of hemoglobin A_{1c} between 7.5% and 8.5% but continues to increase at a slower rate after that.

112. (1) **United Kingdom Prospective Diabetes Study Group** (UKPDS 39). Efficacy of atenolol and captopril in reducing the risk of macrovascular complications in type 2 diabetes. BMJ 1998;317:713–720.

In this report, 758 patients were allocated to tight blood pressure control and 390 patients to conventional blood pressure treatment. The tight blood pressure control group used captopril or atenolol. Captopril treatment did not differ from that using atenolol in relation to controlling blood pressure, macrovascular disease, retinopathy, and hypoglycemia. The group using β-blockers gained 2 kg over an 8-year period in comparison with results in the group using captopril.

113. (1) **United Kingdom Prospective Diabetes Study Group (UKPDS 38)**. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes. BMJ 1998;317:703–713.

In this report, tight blood pressure control of 144/82 mm Hg was associated with 44% less stroke, 37% less microvascular disease, and 32% reduction in death related to diabetes compared with conventional blood pressure control of 154/87 mm Hg.

114. (1) **Brenner BM** et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001;345:861–869.

More than 1,500 patients with type 2 DM were assigned to receive losartan or placebo. After 3.4 years, a 28% risk reduction in end-stage renal disease was seen with the use of losartan.

115. (1) **Lewis EJ** et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001;345:851–860.

More than 1,700 patients with type 2 DM and hypertension were assigned to receive irbesartan or amlodipine or placebo. After a period of 2.6 years, the irbesartan group had better renal outcomes as measured by doubling creatinine levels and diagnoses of end-stage renal disease. The effect of irbesartan was independent of that of lowering blood pressure.

116. (1) **Mann JF** et al. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): A multicentre, randomised, double-blind, controlled trial. Lancet 2008;372(9638):547–553.

In this trial, 25,620 participants were randomly assigned to ramipril 10 mg a day (n = 8,576), telmisartan 80 mg a day (n = 8,542), or to a combination of both drugs (n = 8,502; median follow-up was 56 months), and renal function and proteinuria were measured. The primary renal outcome was a composite of dialysis, doubling of serum creatinine, and death. Analysis was by intention to treat. The number of events for the composite primary outcome was similar for telmisartan (n = 1,147 [13.4%]) and ramipril (1,150 [13.5%]; hazard ratio [HR] 1.00, 95% CI 0.92–1.09), but was increased with combination therapy (1,233 [14.5%]; HR 1.09, 1.01–1.18, p = 0.037). The secondary renal outcome, dialysis, or doubling of serum creatinine was similar with telmisartan (189 [2.21%]) and ramipril (174 [2.03%]; HR 1.09, 0.89–1.34) and more frequent with combination therapy (212 [2.49%]: HR 1.24, 1.01–1.51, p = 0.038). eGFR declined least with ramipril compared with telmisartan (−2.82 [SD 17.2] ml/min/1.73 m^2 vs. −4.12 [17.4], $p < 0.0001$) or combination therapy (−6.11 [17.9], $p < 0.0001$). The increase in urinary albumin excretion was less with telmisartan (p = 0.004) or with combination therapy (p = 0.001) than with ramipril. As such, in people at high vascular risk, telmisartan's effects on major renal outcomes are similar to ramipril. Although combination therapy reduces proteinuria to a greater extent than monotherapy, overall it worsens major renal outcomes.

117. (1) **Pedrini MT** et al. The effect of dietary protein restriction on the progression of diabetic and nondiabetic renal diseases: A meta-analysis. Ann Intern Med 1996;124:627–632.

In this meta-analysis of five studies and 108 type 1 DM patients, low-protein diets significantly reduced the risk of progression to renal failure and death. Low-protein diets also slowed the progression of urinary microalbuminuria.

Intensive Glycemic Management

118. (1) **Wagner VM** et al. Severe hypoglycaemia, metabolic control and diabetes management in children with type 1 diabetes in the decade after the Diabetes Control and Complications Trial: A large-scale multicentre study. Eur J Pediatr 2005;164:73–79.

In this large-scale multicenter study, the incidence of hypoglycemia and glycemic control were investigated in 6,309 children with type 1 diabetes. Young children had more severe hypoglycemic events (31.2/100 patient years) as compared with older children (19.7; 21.7/100 patient years; $p < 0.05$), independent of the treatment regimen. Significant predictors of hypoglycemia were younger age ($p < 0.0001$), longer diabetes duration ($p < 0.0001$), higher insulin dose/kg/d ($p < 0.0001$), injection regimen ($p < 0.0005$), and center experience ($p < 0.05$).

119. (3) **Plank J** et al. Systematic review and meta-analysis of short-acting insulin analogues in patients with diabetes mellitus. Arch Intern Med 2005;165:1337–1344.

This evidence-based meta-analysis compares the effect of treatment with short-acting insulin analogues versus regular insulin on glycemic control, hypoglycemic episodes, quality of life, and diabetes-specific complications. Forty-two randomized controlled trials assessed the effect of analogues versus regular insulin in 7,933 patients with type 1 DM, type 2 DM, and GDM. The difference between A(1c) values obtained using analogues and regular insulin was minimal: −0.12% for adult patients with type 1 DM and −0.02% for patients with type 2 DM. No differences between treatments were observed in children with type 1 diabetes, pregnant women with type 1 DM, and women with gestational diabetes.

120. (1) **Bode B** et al. Comparison of insulin aspart with buffered regular insulin and insulin lispro in continuous subcutaneous insulin infusion: A randomized study in type 1 diabetes. Diabetes Care 2002;25:439–444.

In this study, 146 adult patients with type 1 were randomly assigned to insulin pump treatment with insulin aspart, regular insulin, or lispro for 16 weeks in an open-label, randomized, parallel-group study. Treatment groups had similar baseline A(1c) and after 16 weeks of treatment, A_{1c} values were relatively unchanged from baseline. The rates of hypoglycemic episodes (blood glucose <50 mg/dl) per patient per month were also similar.

121. (1) **Ratner RE** et al. Less hypoglycemia with insulin glargine in intensive insulin therapy for type 1 diabetes: U.S. Study Group of Insulin Glargine in Type 1 Diabetes. Diabetes Care 2000;23:639–643.

This multicenter randomized parallel-group study compared insulin glargine with NPH human insulin in subjects with type 1 diabetes who had been previously treated with multiple daily injections of NPH insulin and regular insulin. In a total of 534 well-controlled subjects with type 1 diabetes, a small and insignificant change A_{1c} levels was noted with insulin glargine (−0.16%) compared with NPH insulin (−0.21%). After the 1-month titration phase, significantly fewer subjects receiving insulin glargine experienced symptomatic hypoglycemia (39.9% vs. 49.2%).

122. (1) **De Leeuw I** et al. Insulin detemir used in basal-bolus therapy in people with type 1 diabetes is associated with a lower risk of nocturnal hypoglycaemia and less weight gain over 12 months in comparison to NPH insulin. Diabetes Obes Metab 2005;7:73–82.

In this multicenter, open-label, parallel-group study, 308 people were randomized to twice-daily insulin detemir or NPH insulin as the basal component of basal-bolus therapy over a period of 12 months. Glycemic control improved in both groups, with HbA(1c) decreasing by 0.64 and 0.56% point in the insulin detemir and NPH insulin groups. No significant difference was apparent between treatments in terms of A(1c). Episodes of nocturnal hypoglycemia during months 2–12 were 32% lower in the detemir group ($p = 0.02$). After 12 months, baseline-adjusted mean body weight was slightly but significantly lower in the insulin detemir group than in the NPH insulin group ($p < 0.001$).

123. (1) **Pickup J** et al. Glycaemic control with continuous subcutaneous insulin infusion compared with intensive insulin injections in patients with type 1 diabetes: Meta-analysis of randomized controlled trials. BMJ 2002;324:705.

In this meta-analysis of 12 randomized controlled trials, 301 people with type 1 diabetes were allocated to insulin infusion, and 299 were allocated to insulin injections. Mean blood glucose concentration was lower in people receiving continuous subcutaneous insulin infusion compared with those receiving insulin injections, equivalent to a difference of 1.0 mmol/l. The percentage of glycated hemoglobin was also lower in people receiving insulin infusion, equivalent to a difference of 0.51%. Blood glucose concentrations were less variable during insulin infusion. This improved control during insulin infusion was achieved with an average reduction of 14% in insulin dose, equivalent to 7.58 U/d, indicating a small difference in glycemic control.

124. (1) **Ratner RE** et al. Amylin replacement with pramlintide as an adjunct to insulin therapy improves long-term glycaemic and weight control in type 1 diabetes mellitus: A 1-year, randomized controlled trial. Diabet Med 2004;21:1204–1212.

In a double-blind, placebo-controlled, parallel-group, multicenter study, 651 patients with type 1 diabetes were randomized to mealtime injections of pramlintide or placebo, in addition to their insulin therapy, for a year. Addition of pramlintide (60 μg three times daily or four times daily) to insulin led to significant reductions in A(1c) from baseline to week 52 of 0.29% ($p < 0.011$) and 0.34% ($p < 0.001$), compared with a 0.04% reduction in placebo group, and was accompanied by a small but significant reduction in body weight from baseline to week 52 of 0.4 kg in pramlintide treatment groups, compared with a 0.8-kg gain in body weight in the placebo group.

125. (1) **Hollander P** et al. Addition of pramlintide to insulin therapy lowers HbA1c in conjunction with weight loss in patients with type 2 diabetes approaching glycaemic targets. Diabetes Obes Metab 2003;5:408–414.

In this pooled post hoc analysis of two randomized trials, investigators showed that adjunctive therapy with pramlintide resulted in significant reductions in both HbA_{1c} and body weight from baseline to week 26 (−0.43% and −2.0 kg differences from placebo, respectively; both $p < 0.001$). These changes were achieved without a concomitant increase in the overall rate of severe hypoglycemic events.

126. (1) **Buse JB** et al. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes. Diabetes Care 2004;27:2628–2635.

This study evaluated the ability of exenatide to improve glycemic control in patients with type 2 diabetes after maximally effective doses of a sulfonylurea failed as monotherapy. In a multicenter placebo-controlled, blinded study, the investigators showed that exenatide significantly reduced A(1c) (by −0.86%) in patients with type 2 diabetes for whom maximally effective doses of a sulfonylurea failed, and that exenatide was associated with (−1.6 kg) weight loss.

127. (1) **Chiasson JL** et al. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: The STOP-NIDDM trial. JAMA. 2003;290:486–494.

In this multicenter double-blind, placebo-controlled, randomized trial, a total of living 1,368 patients were studied for 3.3 years. Patients were randomized to receive either placebo ($n = 715$) or 100 mg of acarbose three times a day ($n = 714$). Three hundred forty-one patients (24%) discontinued their participation prematurely, 211 in the acarbose-treated group and 130 in the placebo group. Decreasing postprandial hyperglycemia with acarbose was associated with a 49% relative risk reduction in the development of cardiovascular events and a 2.5% absolute risk reduction. Acarbose was also associated with a 34% relative risk reduction in the incidence of new cases of hypertension. Even after adjusting for major risk factors, the reduction in the risk of cardiovascular events associated with acarbose treatment was still statistically significant.

128. (2) **Umpierrez GE** et al. Hyperglycemia: An independent marker of in-hospital mortality in patients with undiagnosed diabetes. J Clin Endocrinol Metab 2002;87(3):978–982.

In this study, the medical records of 2,030 consecutive adult patients admitted to a community teaching hospital were reviewed for glucose levels, length of stay, and outcome. Hyperglycemia was present in 38% of patients admitted to the hospital, of whom 26% had a known history of diabetes and 12% had no history of diabetes before the admission. Newly discovered hyperglycemia was associated with higher in-hospital mortality rate (16%) compared with those patients with a history of diabetes (3%) and subjects with normoglycemia (1.7%; both $p < 0.01$). In addition, new hyperglycemic patients had a longer length of hospital stay, a higher admission rate to an intensive care unit, and were less likely to be discharged to home, frequently requiring transfer to a transitional care unit or nursing home facility.

129. (2) **Rassias AJ** et al. Insulin infusion improves neutrophil function in diabetic cardiac surgery patients. Anesth Analg 1998:88:1011–1016.

In this small study of 26 patients, the investigators tested the effect of an insulin infusion on perioperative neutrophil function in patients with diabetes scheduled for coronary artery bypass surgery and found that a continuous insulin infusion and glucose control during surgery improves white cell function in patients with diabetes and may increase resistance to infection after surgery.

130. (2) **Levitan EB** et al. Is nondiabetic hyperglycemia a risk factor for cardiovascular disease? A meta-analysis of prospective studies. Arch Intern Med 2004;164:2147–2155.

In this meta-analysis of 38 prospective reports, cardiovascular disease incidence or mortality was an end point, and blood glucose levels were measured prospectively. Blood glucose level was determined to be a risk marker for CVD among apparently healthy individuals without diabetes.

131. (2) **Bolk J** et al. Impaired glucose metabolism predicts mortality after a myocardial infarction. Int J Cardiol 2001;79:207–214.

In this prospective follow-up trial of 336 consecutive patients with acute myocardial infarction followed up for 14 months, blood glucose was a determinant of mortality. One year mortality

rate was 19.3% and increased to 44% in patients with glucose levels greater than 11.1 mmol/l. The mortality was higher in patients with diabetes than in those without diabetes (40 vs. 16%; $p < 0.05$). Multivariate analysis revealed an independent effect of glucose level on mortality.

132. (2) **Capes SE** et al. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: A systematic overview. Lancet 2000;355:773–778.

In this meta-analysis, the relative risks of in-hospital mortality and congestive heart failure in hyperglycemic and normoglycemic patients with and without diabetes were evaluated by performing a meta-analysis of 15 studies. The authors found that patients without diabetes who had glucose concentrations more than or equal to range of 6.1 to 8.0 mmol/l had a 3.9-fold higher risk of death than did patients without diabetes who had lower glucose concentrations. Glucose concentrations higher than values in the range of 8.0 to 10.0 mmol/l on admission were associated with increased risk of congestive heart failure or cardiogenic shock in patients without diabetes. In patients with diabetes who had glucose concentrations more than or equal to a range from 10.0 to 11.0 mmol/l, the risk of death was moderately increased (1.7), indicating that stress hyperglycemia with MI is associated with an increased risk of in-hospital mortality in patients with and without diabetes.

133. (2) **Furnary AP** et al. Continuous intravenous insulin infusion reduces the incidence of deep sternal wound infection in patients with diabetes after cardiac surgical procedures. Ann Thorac Surg 1999;67:352–360.

In this prospective comparative study of patients with diabetes who underwent open heart surgical procedures, 968 patients were treated with sliding-scale-guided intermittent subcutaneous insulin, and 1,499 were patients treated with a continuous intravenous insulin infusion in an attempt to maintain a blood glucose level of less than 200 mg/dl. Compared with subcutaneous insulin injections, continuous intravenous insulin infusion induced a significant reduction in perioperative blood glucose levels, which led to a significant reduction in the incidence of deep sternal wound infection in the continuous intravenous insulin infusion group (0.8% [12 of 1,499]) versus the intermittent subcutaneous insulin injection group (2.0% [19 of 968]; $p = 0.01$). Multivariate logistic regression revealed that continuous intravenous insulin infusion induced a significant decrease in the risk of deep sternal wound infection ($p = 0.005$; relative risk, 0.34).

134. (2) **Kansagara D**, et al. Intensive insulin therapy in hospitalized patients: A systematic review. Ann Intern Med 2011;154(4):268–282.

This meta-analysis updates our knowledge in relation to intensive insulin therapy.

135. (1) **van den Berghe G** et al. Intensive insulin therapy in the critically ill patients. N Engl J Med 2001;345:1359–1367.

In this landmark prospective, randomized, controlled study, ICU patients were randomly assigned to receive intensive insulin therapy (maintenance of blood glucose at a level between 80 and 110 mg/dl [4.4 and 6.1 mmol/L]) or conventional treatment (infusion of insulin only if the blood glucose level exceeded 215 mg/dl [11.9 mmol/l]) and maintenance of glucose at a level between 180 and 200 mg/dl (10.0 and 11.1 mmol/l). At 12 months, with a total of 1,548 patients enrolled, intensive insulin therapy reduced mortality during intensive care from 8.0% with conventional treatment to 4.6% ($p < 0.04$). The benefit of intensive insulin therapy was attributable to its effect on mortality among patients who remained in the intensive care unit for more than 5 days (20.2% with conventional treatment, as compared with 10.6% with intensive insulin therapy; $p = 0.005$). The greatest reduction in mortality involved deaths due to multiple organ failure with a proven septic focus. Intensive insulin therapy also reduced overall in-hospital mortality by 34%, bloodstream infections by 46%, acute renal failure requiring dialysis or hemofiltration by 41%, the median number of red cell transfusions by 50%, and critical-illness polyneuropathy by 44%; and patients receiving intensive therapy were less likely to require prolonged mechanical ventilation and intensive care. However, caloric intake in this study is different than standard US ICU caloric provision.

136. (1) **Pittas AG** et al. Insulin therapy for critically ill hospitalized patients: A meta-analysis of randomized controlled trials. Arch Intern Med 2004;164:2005–2011.

In this meta-analysis of 35 randomized controlled trials, insulin therapy decreased short-term mortality by 15% (relative risk [RR], 0.85). In subgroup analyses, insulin therapy also decreased mortality in the surgical intensive care unit (RR, 0.58), when the aim of therapy was glucose control (RR, 0.71), and in patients with DM (RR, 0.73).

137. (2) **Moghissi ES** et al. American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. Endocr Pract 2009;15(4):353–369.

138. (1) **Dickerson LM** et al. Glycemic control in medical in patients with type 2 diabetes mellitus receiving sliding scale insulin regimens versus routine diabetes medications: A multicenter randomized controlled trial. Ann Fam Med 2003;1:29–35.

In this study of 153 hospitalized patients with type 2 DM, the investigators used an insulin sliding-scale regimen that was adjusted to individual patients and was accompanied by an antidiabetic agent for background/basal coverage. In this form, insulin sliding scale did not perform better than standard treatment, and no significant differences were found between the group treated with conventional treatment and the group treated with sliding scale combined with some form of antidiabetic basal coverage. Although this is a small study, it shows that insulin sliding scale can be used safely in certain situations.

139. (1) **Buse JB** et al. Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial: Design and methods. Am J Cardiol 2007;99(12);21i–33i.

This was a large study of 10,251 subjects with type 2 diabetes (median HbA1c 8.1%) and a history of CVD. Intervention was aimed at obtaining a goal A1c of less than 6% in the tight control group versus conventional therapy (goal A1c of 7.0%–7.9%). Surprisingly, after an interim analysis at 3.5 years of follow-up, the study was stopped because of an increased risk of overall mortality (5.0% vs. 4.0%, $p = 0.04$).

140. (1) **Duckworth WC** et al. The duration of diabetes affects the response to intensive glucose control in type 2 subjects: The VA Diabetes Trial (VADT). J Diabetes Complications2011;25(6):355–361.

This is a large study with 1,791 veterans with type 2 diabetes with suboptimal glucose control. Intervention was associated with an absolute HbA1c reduction of 1.5% between the intervention and conventional groups. After a follow-up period of 5.6 years, the study found no difference in CV events between the two groups (death from CVD 4.5% vs. 3.7%, death from any cause 11.4% vs. 10.6%).

141. (1) **ADVANCE Management Committee**. Study rationale and design of ADVANCE: Action in diabetes and vascular disease—preterax and diamicron MR controlled evaluation. Diabetologia 2001;44:1118–1120

In this large multicenter randomized study, 11,140 type 2 DM patients were randomized to either standard glucose control or intensive glucose control, using gliclazide (modified release) and other drugs to achieve a glycated hemoglobin value of 6.5% or less. The primary end points were composites of major macrovascular events and major microvascular events intensive (very tight) glucose control, involving gliclazide (modified release) and other drugs that lowered the glycated hemoglobin to 6.5%, was associated with a 21% relative reduction in nephropathy.

7

Lipid Disorders

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Coronary heart disease (CHD) is the major cause of mortality in industrialized nations, and despite impressive advances in cardiovascular care, the adverse event rates remain significant. Dyslipidemia is an important risk factor for the development and progression of atherosclerotic cardiovascular disease (ASCVD) [1], and diagnosis and treatment of patients with lipid disorders have been shown to significantly reduce the risk of future cardiac adverse outcomes. The intensity of risk-reduction therapy should be adjusted to the individual's absolute risk [2], and the accurate assessment of the patient's overall cardiovascular risk status is the central component for the optimal treatment of individuals with dyslipidemia (*Grade A*).

Lipid disorders can be classified into primary (genetic or inherited) (Table 7.1) or secondary (due to disease or environmental factors). Important secondary factors that result in altered lipid metabolism include hypothyroidism, diabetes mellitus, renal disease, obstructive liver disease, alcohol intake, and various medications, and the identification and modification of these secondary causes should be aggressively pursued.

LIPOPROTEIN METABOLISM

Lipoproteins are large complexes that transport lipids (mainly cholesterol esters, triglycerides [triacylglycerol; TAG], and fat-soluble vitamins) to and from the vasculature to various body tissues. The plasma lipoproteins are divided into five main classes based on their relative densities: chylomicrons, very-low-density lipoproteins (VLDLs), intermediate-density lipoproteins (IDLs), low-density lipoproteins (LDLs), and high-density lipoproteins (HDLs).

Lipoprotein metabolism occurs through two basic mechanisms, which include the transport of dietary lipids to the liver and peripheral tissues (exogenous pathway) and the production and delivery of hepatic lipids into the circulation and peripheral tissues (endogenous pathway) [3]. In the exogenous pathway, dietary cholesterol is acted upon by the intestinal cells to form cholesterol esters through the addition of fatty acids. TAGs from the diet are hydrolyzed by pancreatic lipases within the intestine and emulsified with bile acids to form micelles.

Table 7.1. Inherited Lipid Disorders

Condition	Mechanisms/Characteristics
Familial combined hypercholesterolemia (FCHL)	The most common primary lipid disorder may affect ≤2% of US population. Autosomal dominant. Increased secretion of apo B-100 with resulting in varying patterns of high LDL with moderate elevations of TAG and low HDL. Significantly increased risk of ASCVD. Common comorbidities include diabetes, hypertension, and obesity
Familial hypertriglyceridemia (FHTG)	Relatively common (1 in 500). Autosomal dominant. Usually with moderately to severely elevated TAG (250–1,000 mg/dl) with mildly increased cholesterol (<250 mg/dl) with low HDL due mainly to increased production and impaired clearance of VLDL, although more severe form has elevated chylomicrons
Familial hypercholesterolemia (FHC)	Occurs in 1 in 500. Deficient or defective LDL receptor resulting in reduced clearance and accumulation of LDL with normal TAG. Autosomal dominant. Heterozygous FHC (LDL range, 325–450 mg/dl). Homozygous FHC with very high LDL (500–1,000 mg/dl). Clinical clues include tendon xanthomas, childhood CHD, arcus cornea in young patients, premature ASCVD
Primary (familial) hypoalphalipoproteinemia	Most common genetic cause of low HDL. HDL <10th percentile with normal cholesterol and TAG levels after secondary causes of low HDL are excluded. Increased risk of premature ASCVD
Familial defective apo B-100	Occurs in 1 in 1,000. Autosomal dominant. Moderate elevation in LDL with normal TAG. Mutant apo B-100 poorly recognized by LDL receptor. Palmar and tuberoeruptive xanthomas, premature ASCVD. Clinically resembles heterozygous FHC
Familial dysbetalipoproteinemia (FDBL)	Occurs in 1 in 10,000. Mixed hyperlipidemia due to increased chylomicrons and VLDL remnants due to defective apolipoprotein E. Autosomal dominant. Tendon xanthomas, premature ASCVD
Familial chylomicronemia syndrome (FCS)	Occurs in ~1 in 1,000,000. Autosomal recessive. Genetic deficiency of lipoprotein lipase or cofactor apo C-II resulting in extremely high TAG (>1,000 mg/dl) due to chylomicronemia. Recurrent pancreatitis, lipemia retinalis, eruptive xanthomas, hepatomegaly. Usually *without* premature ASCVD
Tangier disease	Rare disease manifested by very low HDL due to mutations in the gene *ABCA1* results in rapid clearance of HDL from the circulation. Patients have cholesterol accumulation in the reticuloendothelial system with hepatomegaly and pathognomonic enlarged yellowish orange tonsils
Lecithin-cholesterol Acyltransferase (LCAT) deficiency	Rare disorder of low HDL due to lecithin/cholesterol acyltransferase deficiency. Increased catabolism of HDL. Corneal opacities due to accumulation of cholesterol in lens ("fish-eye disease")

Longer-chain fatty acids are incorporated into TAGs and complexed with other particles such as cholesterol esters and phospholipids to form chylomicrons (which have a high concentration of TAGs). These particles are acted on by lipoprotein lipase along the capillary endothelium, and the TAGs are hydrolyzed, releasing free fatty acids, most of which are taken up by adjacent adipocytes or myocytes, and the remaining particles (chylomicron remnants) are transported to the liver. In the endogenous pathway, VLDL is transformed into IDL and then into LDL through hepatic metabolism. VLDL particles are similar to chylomicrons but have a higher ratio of cholesterol to TAGs and contain apolipoprotein B-100. The TAG of VLDL is hydrolyzed by lipoprotein lipase, and the particles continue to become smaller and denser and transform into IDL, which is composed of similar amounts of cholesterol and TAG. The hepatic cells remove approximately half of VLDL remnants and IDL. The remainder of IDL is modified by hepatic lipase to form LDL. LDL is composed of a core of primarily cholesterol esters, surrounded by a surface of phospholipids, free cholesterol, and apolipoprotein B. The majority of circulating LDL is cleared through LDL-mediated endocytosis in the liver. Modified (oxidized) plasma LDL accumulates in the intima and is acted on by activated macrophages (foam cells) and through complex mechanisms involving cytokines, growth factors, smooth cell proliferation, and inflammation, and results in atheroma formation [4]. The process of transferring cholesterol from peripheral cells to the liver for removal from the body by biliary secretion is called reverse cholesterol transport. The role of HDL in enhancing reverse cholesterol transport is one of the mechanisms by which HDL protects against the process of atherosclerosis. The major protein of HDL is apo A-I.

The major lipid abnormalities of clinical significance result in an alteration in the levels of LDL, HDL, and TAG, and these disorders are the primary focus of this chapter. Other associated abnormalities that have been investigated include abnormal levels of serum lipoprotein(a) and homocysteine, although the data surrounding these and other emerging risk factors remain controversial [5].

LOW-DENSITY LIPOPROTEIN CHOLESTEROL

Trials

The largest body of evidence exists for improved outcomes with LDL lowering, and thus, LDL remains the major therapeutic target for intervention [2]. Large epidemiologic studies such as the Seven Countries Study [6] confirmed the association of total serum cholesterol and CHD. In addition, the Multiple Risk Factor Intervention Trial [7] demonstrated that this relation was continuous and graded, without a threshold level. Large, placebo-controlled, randomized trials confirmed the benefit of LDL lowering on reducing long-term cardiac event rates [8–10].

Primary Prevention Trials

The central principle of management of the patient without established atherosclerotic vascular disease is that the intensity of risk reduction should be commensurate with the individual's absolute cardiovascular risk (Table 7.2) (*Grade A*). The major risk factors (exclusive of LDL cholesterol) include age older than 45 years in men and older than 55 years in women, cigarette smoking, hypertension (defined as ≥140/90 mm Hg or on antihypertensive medication), low HDL cholesterol (<40 mg/dl), and a family history of premature CHD in first-degree relatives (younger than 55 years in male relative, and younger than 65 years in female relative) [2]. The LDL cholesterol is not included among the risk factors because the reason for assessing these risk factors is to treat the LDL. A high HDL (≥60 mg/dl) is regarded as a "negative" risk factor and removes one other risk factor from the total count.

Table 7.2. Updated ATP III LDL-C Goals and Cut-Points for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories

Risk Category	LDL-C Goal (mg/dl)	Initiate TLC (mg/dl)	Consider Drug Therapy (mg/dl)
High risk: CHD or CHD risk equivalents (10-year risk, >20%)*	<100 mg/dl (optimal goal <70 mg/dl)†	≥100 mg/dl‡	≥100 mg/dl (<100 in selected high-risk populations)†
Moderately high risk: 2+ risk factors (10-year risk, 10%–20%)**	<130 mg/dl	≥130 mg/dl	≥130 mg/dl (100–129, consider drug options)††
Moderate risk: 2+ risk factors (10-year risk, <10%)	<130 mg/dl	≥130 mg/dl	≥160 mg/dl
Low risk: 0–1 risk factors	<130 mg/dl	≥160 mg/dl	≥190 mg/dl (160–189, LDL-lowering drug optional)

*CHD includes established coronary artery disease (history of myocardial infarction, unstable or stable angina, coronary revascularization, or evidence of clinically significant myocardial ischemia). CHD equivalents include diabetes and evidence of noncoronary atherosclerosis (peripheral arterial disease, abdominal aortic aneurysm, carotid artery disease, transient ischemic attacks or stroke.

†Very high risk favors the optional LDL-C goal of 70 mg/dl and in patients with high triglycerides and low HDL.

‡In individual at high risk or moderately high risk with lifestyle-related risk factors (i.e., obesity, physical inactivity, elevated triglyceride, low HDL, metabolic syndrome), aggressive therapeutic lifestyle changes to modify these risk factors are advisable regardless of the LDL level.

**Risk factors include: age (men >45 years, and women >55 years), hypertension (BP >140/90 mm Hg or taking antihypertensive medication), smoking, low HDL (<40 mg/dl), and family history of premature CAD (CHD in male first-degree relative <55 years; CHD in female first-degree relative <65 years).

††For moderately high-risk individuals, if the LDL is 100–129 mg/dl at baseline or on TLC, initiation of an LDL-lowering drug to achieve an LDL of <100 mg/dl is a therapeutic option.

The patient's risk is estimated first by determining the number of risk factors. The first group comprises patients with none to one risk factor. Traditionally, this group has been assigned to a low-risk category (10-year risk of CHD, <10%), and the recommended LDL goal has been less than 160 mg/dl (*Grade A*). However, a very high LDL (>190 mg/dl) may warrant consideration of drug therapy to reduce long-term risk (*Grade D*). In addition, a single powerful risk factor (strong family history of premature CHD, heavy cigarette smoking, very low HDL, poorly controlled hypertension) favors the use of drugs to reduce the LDL (*Grade D*).

The second group of patients comprises those with two or more risk factors. The 10-year risk of a cardiac event is assessed by using the Framingham scoring, which takes into account the patient's age, gender, HDL, blood pressure, smoking

status, and family history of premature ASCVD, and may be calculated by using tables or handheld and Internet-based online calculators (www.nhlbi.nih.gov/guidelines/cholesterol). Framingham scoring stratifies persons with multiple risk factors into those with a 10-year risk of CHD of more than 20%, 10% to 20%, or less than 10%. The LDL goal of patients with multiple (2+) risk factors and a 10-year risk of 10% to 20% has traditionally been less than 130 mg/dl [2], but an LDL goal of less than 100 mg/dl is a therapeutic option based on updated clinical guidelines [11], and drug therapy (in addition to therapeutic lifestyle changes) should be considered to achieve this goal (*Grade A*). Patients with multiple risk factors that confer a risk for a major cardiac event of more than 20% over a 10-year period are at highest risk and are treated as if they had established cardiovascular disease (*Grade A*).

A patient's overall risk may be affected by other factors not included in major factors outlined earlier. Other risk factors that should be taken into consideration include obesity, sedentary lifestyle, and an atherogenic diet, which are excellent targets for clinical intervention (*Grade C*). Other emerging risk factors such as lipoprotein(a), proinflammatory markers, and impaired fasting glucose further guide the intensity of risk reduction in selected individuals (*Grade A*). Specifically, an elevated high-sensitivity C-reactive protein (hs-CRP) has been touted as a potentially useful marker for identifying individuals of higher risk who may benefit from more intensive lowering of LDL (*Grade A*). In addition, LDL subclasses may be measured through nuclear magnetic resonance (NMR) spectroscopy, and the detection of smaller, denser LDL particles may provide incremental information on cardiovascular risk [12]. Furthermore, the metabolic syndrome is a constellation of interrelated metabolic risk factors with underlying insulin resistance that imparts an especially high risk for the development of ASCVD and diabetes (*Grade A*) [11].

The WOSCOPS trial [13] enrolled middle-aged men with hypercholesterolemia (mean total cholesterol, 272 mg/dl) and no history of myocardial infarction (MI) to treatment with pravastatin and found a significant reduction in death or nonfatal MI by 31% compared with placebo over a mean follow-up of 4.9 years. The ASCOT-LLA trial [14] evaluated treatment with atorvastatin in hypertensive patients with modest hypercholesterolemia (total cholesterol, <240 mg/dl) compared with placebo. After a median follow-up of 3.3 years, the trial was stopped prematurely because of a highly significant 36% reduction in fatal CHD and nonfatal MI, which became apparent in the first year of follow-up. The ALLHAT trial [15] was a similar study that evaluated the administration of pravastatin in the treatment of older, hypertensive, moderately hypercholesterolemic (mean total cholesterol, 244 mg/dl, and mean LDL, 148 mg/dl) patients with one additional risk factor compared with placebo with a mean follow-up of 4.8 years. The results of this trial showed that no statistically significant differences in mortality or CHD event rates existed, although this may have been due to the high rate of nonstudy statin in the usual-care group or the modest differential in total cholesterol and LDL between the pravastatin and usual-care group compared with prior statin trials. The AFCAPS/TeXCAPS trial [16] enrolled patients without CHD and with average serum cholesterol levels (mean total cholesterol, 221 mg/dl, and mean LDL, 150 mg/dl) and below-average HDL (mean HDL, 36 mg/dl) levels to lovastatin and demonstrated a reduction in the first acute major coronary event (MI, unstable angina, or sudden cardiac death) by 37% [16].

The JUPITER trial [17] enrolled 17,802 patients without known CHD with normal LDL levels (mean LDL 108 mg/dl) and elevated high-sensitivity C-reactive protein greater than 2.0 mg/l (median hs-CRP of 4.2 mg/l) to 20 mg of rosuvastatin or placebo. Patients were followed for a median of 1.9 years, and the

patients treated with rosuvastatin had statistically significant 44% decrease in the primary composite end point of cardiac death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina, or coronary revascularization compared with placebo. This trial suggests a role for intensive lowering of LDL with statin therapy in apparently healthy men and women with an elevated hs-CRP and remains an area of ongoing research (*Grade A*).

Taken in aggregate, these landmark clinical trials [10,13–16] suggest that lipid-lowering therapy in intermediate- to high-risk patients without established ASCVD with moderate hypercholesterolemia is beneficial and is associated with lower adverse major cardiac event rates on follow-up (*Grade A*).

Secondary Prevention Trials

The highest-risk group includes those patients with established cardiovascular disease or a "CHD risk equivalent." This group comprises patients with known coronary artery disease, other clinical forms of atherosclerotic vascular disease, including peripheral vascular disease, carotid artery disease, abdominal aortic aneurysm, and diabetes mellitus, and patients with multiple risk factors that confer a risk for a major cardiac event of more than 20% over a 10-year period. The identification of subclinical atherosclerotic disease such as high coronary calcification, significant carotid intimal medial thickness, or significant atherosclerotic burden on CT angiography likewise warrants aggressive and intensive lipid lowering.

The 4S trial [8] was the first trial to demonstrate a reduction in total mortality (30% relative risk reduction) in middle-aged patients with high cholesterol (mean total cholesterol, 272 mg/dl, and mean LDL, 190 mg/dl) with established CHD treated with simvastatin compared with placebo, in addition to reducing major coronary events and coronary revascularization, over an average of 5.4 years. The CARE [10] trial extended these findings and to patients with established CHD and "average" cholesterol levels (mean total cholesterol, 209 mg/dl, and mean LDL, 139 mg/dl) and demonstrated a 24% relative risk reduction in the primary end points (mortality and major cardiac event rates and stroke). The LIPID trial [9] was the largest trial of secondary prevention and similarly demonstrated a 24% reduction in CHD mortality, as well as total mortality and fatal and nonfatal MI. The Heart Protection Study [18] demonstrated a reduction in all-cause mortality with treatment with simvastatin in a wide range of high-risk patients (coronary artery disease, occlusive arterial disease, or diabetes), irrespective of their baseline LDL level. Importantly, a significant reduction was noted in nonfatal MI, stroke, and coronary and noncoronary revascularization, and the risk reductions were similar and significant, even in patients with a "low" baseline LDL level (<116 mg/dl), suggesting that lower is better. In summary, these large, randomized clinical trials clearly demonstrated that lipid-lowering therapy with statins in patients with established ASCVD resulted in a highly significant reduction in mortality and cardiac events over a wide range of LDL values (*Grade A*).

How Low Should You Go?

The Heart Protection Study [18] and the PROVE IT trial [19] showed incremental 22% and 16% reductions in risk for adverse cardiac events with LDL levels reduced to less than 100 mg/dl. The Treat To New Targets (TNT) trial [20] demonstrated a 22% relative and a 2.2% absolute risk reduction of more major cardiac events (including death from CHD, nonfatal MI, resuscitation after a cardiac arrest, and fatal or nonfatal stroke) in the group receiving high-dose atorvastatin compared with the low-dose group. The mean LDL in the high-dose group was 77 mg/dl compared with 101 mg/dl in the low-dose group. Overall, these data suggest

that no clear-cut identifiable threshold exists for LDL level for risk reduction and that "lower is better." Based on these recent trials demonstrating reduced cardiovascular event rates with lower LDL levels, the current recommendation for optimal LDL is less than 70 mg/dl in patients at very high risk (*Grade A*) [11]. The factors that place a patient at very high risk include established ASCVD and CHD equivalents, multiple major risk factors, and severe and poorly controlled risk factors (i.e., smoking). No major safety issues have been identified thus far with reducing LDL to the range of 50 to 70 mg/dl [21]. The current evidence from the major clinical trials to date favors LDL lowering primarily with a statin as the initial therapeutic strategy (*Grade A*).

Treatment Options

Dietary Modification

Lifestyle and dietary modifications remain crucial, and reduced intake of saturated fat and cholesterol, increased physical activity, and weight control for all patients are recommended. All patients should be advised to adopt therapeutic lifestyle changes including reduced intake of saturated fats (<7% of total calories) and cholesterol (<200 mg/d), increased intake of soluble fiber (10–25 g/d), weight reduction, and increased physical activity (*Grade A*). Dietary modification should be a mainstay of any LDL-lowering strategy; however, the average LDL reduction from diet alone is in the range of 5% to 10% [22], and compliance with a strict diet remains problematic in routine clinical practice.

Statins (3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase Inhibitors)

Statins reduce serum LDL levels through intracellular inhibition of the rate-limiting step in cholesterol production, which reduces cholesterol biosynthesis in the liver and upregulates LDL-C receptors to increase clearance of LDL-C from the blood. The statins reduce the LDL by 18% to 55%, increase HDL by 5% to 15%, and reduce TAG by 7% to 30% (Table 7.3). At the current available doses, rosuvastatin and atorvastatin are the most potent statins, followed in order of LDL-reducing potency by simvastatin, lovastatin, pravastatin, and fluvastatin. Each doubling of a statin dose achieves an approximately 6% additional reduction in serum LDL (the "rule of 6s"). A large meta-analysis involving 14 randomized, placebo-controlled trials involving 90,056 patients showed that lowering LDL cholesterol levels by 39 mg/dl (1 mmol/l) with statin therapy significantly reduces the 5-year risk of major coronary events, coronary revascularization, and stroke by 21% [23]. This benefit emerged early, was sustained, and was related mainly to the individual's absolute risk and to the absolute reduction in LDL cholesterol levels achieved.

Statin Therapy in High-Risk Populations

Statins have clearly been shown to be beneficial in a wide range of high-risk populations including acute coronary syndromes [19,24,25], diabetics [26,27], and the elderly [28]. In contrast, the treatment of patients with advanced renal disease and hemodialysis has been particularly problematic, and statin therapy had a neutral effect of cardiovascular outcomes, likely due to the advanced atherosclerotic burden and the risk of competing cardiovascular events and renal complications. The CARDS trial evaluated the effect of treatment with atorvastatin (20 mg/d) in 1,255 subjects with type 2 diabetes mellitus receiving hemodialysis, and no significant difference was found in the primary end point (composite of death from cardiac causes, nonfatal MI, and stroke) in the atorvastatin group compared with placebo (relative risk, 0.92; 95 CI, 0.77–1.10; $p = 0.37$) after a median follow-up of 4 years [27]. Similar

Table 7.3. FDA-Approved Drugs for Treating Lipoprotein Abnormalities

Drugs	Lipid Effects	Adverse Effects/Drug Interactions
Statins		
Pravastatin (40–80 mg qhs) Lovastatin (20–80 mg qhs) Fluvastatin (20–80 mg qhs) Simvastatin (20–80 mg qhs) Atorvastatin (10–80 mg qhs) Rosuvastatin (10–40 mg qhs)	LDL: ↓18%–55% HDL: ↑5%–15% TAG: ↓7%–30%	Increased risk of myopathy with itraconazole, ketoconazole, erythromycin, clarithromycin, erythromycin, HIV protease inhibitors, nefazodone, amiodarone, verapamil, or large quantities of grapefruit juice (>1 quart daily); may raise hepatic transaminase levels
Cholesterol-absorption inhibitor		
Ezetimibe (10 mg qd)	LDL: ↓15%–20% HDL: ↑2%–5% TAG: ↓3%–8%	Side effects include headache and diarrhea; myopathy and hepatitis rare
Fibric acids		
Gemfibrozil (600 mg b.i.d.) Fenofibrate (48–145 mg or 43–130 mg qd)	LDL: ↓5%–20% HDL: ↑10%–20% TAG: ↓20%–55%	Side effects include rash and dyspepsia; potentiates the action of warfarin; contraindicated in patients with gallstones or severe renal insufficiency/hemodialysis; variable effects of the serum LDL, and may increase LDL
Nicotinic acids		
Immediate release (100 mg t.i.d. to 2 g t.i.d.) Sustained release (250 mg b.i.d. to 1.5 g b.i.d.) Extended release (500 mg qhs to 2 g qhs)	LDL: ↓5%–20% HDL: ↑15%–35% TAG: ↓20%–50%	Most common side effect is flushing; potentiates the action of warfarin; may precipitate acute gout and esophageal reflux, hyperglycemia
Bile acid sequestrants		
Cholestyramine (4–24 g/d) Colestipol (5–40 g/d) Colesevelam (3,750–4,375 mg qd)	LDL: ↓15%–30% HDL: ↑3%–5% TAG: ↑3%–10%	Common side effects include nausea, constipation, and bloating; associated with increased TAG levels
Fish oils		
Omega-3 fatty acid (3–12 g)	LDL: ↑45% HDL: ↑9% TAG: ↓45%	Associated with increased LDL level; side effects include dyspepsia and fishy aftertaste

findings were demonstrated in the AURORA trial, which enrolled patients with advanced chronic kidney disease (CKD) on hemodialysis randomized to rosuvastatin versus placebo, and failed to show a significant decrease in mortality or CHD events despite lowering the LDL, CRP, and total cholesterol [29]. In contrast, the SHARP trial [30] enrolled patients with CKD (a third of patient were on hemodialysis) and randomized to simvastatin plus ezetimibe versus placebo and demonstrated a statistically significant decrease in CHD events in simvastatin and ezetimibe group.

Pleiotropic Effects of Statins

Although treatment with statins has resulted in major reductions in cardiac event rates, the amount of plaque regression demonstrated has been modest at most [31,32], raising the possibility that the beneficial effects extend over and beyond LDL lowering. The pleiotropic effects of statins include anti-inflammatory, antithrombotic, immunomodulatory, and vascular effects, although the precise mechanisms remain elusive [33].

Safety Issues

Statins are generally well tolerated; however, common minor side effects include muscle and joint aches (≤5%), fatigue, dyspepsia, and headaches. More serious side effects such as severe myositis with generalized muscle pain and weakness and elevated creatine kinase (rarely leading to rhabdomyolysis and acute renal failure) or severe hepatitis may occur infrequently. Adverse drug interactions should be carefully monitored (Table 7.3), particularly at higher doses and in elderly patients with low body weight and patients with impaired renal function or receiving combination therapy with fibrates and/or nicotinic acid [34]. Liver transaminases should be checked before starting therapy and with increases in dosage. High elevations of liver transaminases (>3 times the upper limit of normal) are exceedingly rare and usually resolve completely after discontinuing the statin. Milder increases in liver function tests (1–3 times the upper limit of normal) require close monitoring but do not necessarily require stopping the drug in the absence of symptoms [35].

Ezetimibe (Zetia)

Ezetimibe acts through inhibition of intestinal cholesterol absorption in the small intestine, leading to a reduction in hepatic cholesterol stores and increasing clearance of cholesterol from the blood. As monotherapy, ezetimibe effectively decreases LDL by 15% to 20% [36]. The combination of absorption pathway in the small intestine with ezetimibe and a statin results in dual inhibition through inhibition of the production pathway and the production pathway in the liver, respectively, reducing the LDL by as much as an additional 25%, with potentially fewer side effects [37]. These impressive reductions in LDL however have not translated into improved clinical surrogate markers (i.e., carotid intimal thickness) in the large, randomized clinical trials to date, raising the concern that mechanism by which the LDL is lowered rather than LDL lowering itself that may be the crucial component in determining its overall clinical efficacy. The ENHANCE trial [38] enrolled patients with familial hyperlipidemia (median LDL 318 mg/dl) to simvastatin plus ezetimibe versus simvastatin monotherapy. The study demonstrated a statistically significant decrease in LDL in the ezetimibe group; however, there was no statistically significant decrease in carotid intima-media thickness. The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) is an ongoing, large, randomized study that will evaluate the effects of ezetimibe and simvastatin on clinical cardiovascular events.

Bile Acid Sequestrants (Resins)

Bile acid sequestrants act through binding bile acids in the intestine, resulting in increased excretion in the stool, stimulating greater intrahepatic cholesterol utilization for bile acid synthesis. This results in upregulation of the LDL receptor, which enhances clearance of LDL in the bloodstream. In general, resins reduce LDL by 15% to 30%. The available bile acid sequestrants include cholestyramine, colesevelam, and colestipol. Treatment with cholestyramine has been associated with a reduction in progression of atherosclerosis compared with control [39]. Because resins are not systemically absorbed, they are extremely safe but are associated with side effects such as nausea, constipation, and bloating. Other medications should be taken either 1 hour before or 4 hours after the resins because of binding and decreased absorption (i.e., warfarin, digoxin). Resins may significantly increase the TAG level and should be avoided in patients with hypertriglyceridemia.

Nicotinic Acid and Fibric Acids

Nicotinic acid and fibric acid modestly reduce LDL (~5%–20%) and are used mainly as therapies to reduce TAG and increase LDL and are discussed in detail later in the chapter under Treatment Options for HDL/TAG.

Combination Therapy

Even with the most potent statins, achieving the target LDL is often challenging with monotherapy. Higher doses of statins are associated with higher-risk myopathy and hepatotoxicity. Combination therapy with a statin with ezetimibe has a synergistic mechanism of action by inhibiting dual pathways. Because of the increasing prevalence of diabetes and insulin resistance with several metabolic abnormalities, combination therapy is often the optimal approach for achieving the desired results by targeting multiple lipoprotein particles and metabolic pathways (*Grade A*) [40]. The ARBITER-6 HALTS [41] trial randomized patients with known CVD on statin therapy (LDL < 100 mg/dl; HDL < 50 mg/dl) to ezetimibe versus extended-release niacin. The trial demonstrated statistically significant decrease in carotid intima-media thickness with niacin treatment but no difference in thickness with ezetimibe. Thus, combination therapy with a statin and niacin [42,43], or a statin and a fibrate [44], or all three together, may the preferred strategy, particularly with markedly abnormal HDL and TAG levels, although safety issues remain a concern (*Grade A*).

Nonpharmacologic Strategies

LDL apheresis involves the direct removal of LDL from the plasma and may be the preferred option in severe drug-resistant or refractory hyperlipidemia (*Grade C*). Partial ileal bypass surgically depletes the enterohepatic supply of bile acids, resulting in upregulation of the LDL receptor in the liver and increasing LDL clearance, and may be an option in patients with severely elevated LDL and normal TAG refractory to maximal medical management who are not candidates for LDL apheresis (*Grade C*).

HIGH-DENSITY LIPOPROTEIN CHOLESTEROL AND TRIGLYCERIDES

Although LDL remains the primary lipid-lowering priority, low HDL and high TAG have been associated with increased cardiac risk and are potential targets for therapeutic intervention. A meta-analysis [45] suggested that a TAG elevation of 89 mg/dl is associated with a 14% risk in coronary risk in men and 37% risk in women after adjustment for HDL, although other studies have not found independent risk [46]. TAG has great variability and may be affected by recent

weight change, exercise status, or consumption of carbohydrates or alcohol, and medications such as estrogen and isotretinoin. The recommended TAG goal is less than 150 mg/dl (*Grade A*) [2]. "Non-HDL" is equal to total cholesterol minus the HDL and represents the spectrum of atherogenic apolipoprotein B (apo B)–carrying lipoproteins including VLDL, chylomicron remnants, VLDL remnants, IDL, lipoprotein(a), and LDL. If TAG levels are 200 mg/dl or more, non-HDL is a secondary target of treatment after the LDL goal has been achieved. The non-HDL goal is 30 mg/dl higher than the specified goal for LDL (*Grade D*) (Table 7.2). If the TAG levels are 500 mg/dl or more, then treatment of TAG takes priority over LDL reduction because of the desire to reduce the risk of acute pancreatitis (*Grade D*).

Epidemiologic data clearly suggest that a low HDL may be a significant risk factor comparable to and independent of an elevated LDL [47]. A low HDL has been defined as less than 40 mg/dl in men and less than 50 mg/dl in women. A "high" HDL is more than 60 mg/dl, although the classification of the "optimal" HDL will continue to evolve.

Pooled data from several studies estimate a 2% to 3% reduction in cardiovascular risk for every 1-mg/dl increase in HDL [48]. The potential mechanisms of action whereby HDL delays the development and progression of atherosclerosis include reverse cholesterol transport, anti-inflammatory activity, and antioxidant effects [49]. Limited data exist on the benefits of elevating HDL through pharmacologic intervention, although this may be because currently available agents achieve only moderate increases in HDL. The metabolic syndrome and diabetes mellitus, because of their similar pathophysiology, are associated with low HDL and high TAG and are relatively common causes of these disorders. The genetic disorders resulting in elevated TAG and low HDL are outlined in Table 7.1.

Treatment Options

Therapeutic Lifestyle Changes

HDL levels have been shown to increase with weight reduction, regular aerobic exercise, modest alcohol consumption, and smoking cessation. Typically, one may expect a 1-mg/dl increase in HDL for every 3-kg weight loss. Regular aerobic exercise may increase HDL by 10% to 20% in sedentary adults.

Nicotinic Acid (Niacin)

Nicotinic acid, or niacin, is a B-complex vitamin that increases HDL by 15% to 35% and decreases TAG by 20% to 50%. Niacin increases HDL through metabolic pathways that increase the pre-B, apo A-I–rich HDL particles, which are the cardioprotective subfraction of HDL. The Coronary Drug Project showed that treatment with niacin reduced the risk of nonfatal MI, even after 15 years of follow-up [50]. The most common side effect is cutaneous flushing, and this may be diminished by increasing the dose gradually, prescribing the drug with meals or at bedtime, and by taking aspirin or ibuprofen 30 minutes beforehand. The major adverse side effect of niacin is hepatotoxicity. The effect of the novel combination of niacin and laropiprant (a prostaglandin D2 receptor 1 antagonist, which decreases the flushing side effect of niacin) on cardiovascular clinical outcomes is currently being evaluated in the large, randomized Heart Protection Study 2—Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) trial.

Fibric Acids (Fibrates)

Fibrates are agonists of PPARα, which is a nuclear receptor involved in the modulation of lipid and carbohydrate metabolism. Fibrates increase hydrolysis of TAG by enhancing lipoprotein lipase activity, increase clearance of TAG-rich

lipoproteins from the plasma, and decrease the rate of release of free fatty acids from adipocytes. Fibrates are the most effective agents for reducing TAG (20%–55%) and also effectively increase HDL (10%–20%). These agents have variable effects of the serum LDL, and treated patients with hypertriglyceridemia may have an increase in their LDL. Fibrates are the drug of choice in patients with severe hypertriglyceridemia (>1,000 mg/dl) (*Grade A*). The common side effects and adverse interactions of fibrates are outlined in Table 7.3.

Fibrates have been shown to be beneficial in both primary prevention [51] and in patients with established CHD [46]. The VA-HIT trial compared treatment with gemfibrozil with that with placebo in men with established CAD and average LDL levels (<140 mg/dl) and low HDL (<40 mg/dl). After a mean follow-up of 5 years, gemfibrozil decreased TAG levels by 31% and increased HDL by 6%, whereas levels of LDL remained quantitatively unchanged. A relative risk reduction of 22% was seen in CHD death and nonfatal MI. Surprisingly, fenofibrate failed to reduce the primary end point (CHD death or nonfatal MI) significantly compared with placebo in 9,795 diabetic patients in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial, although the authors suggested that the higher rate of starting statin therapy in patients allocated to placebo might have attenuated a moderately larger treatment benefit [52].

Statins

Statins typically result in only a modest increase in HDL, and this effect appears to be independent of LDL-reducing capacity. Simvastatin (8%–16% increase), rosuvastatin (8%–14%), and pravastatin (2%–12%) are the most potent HDL-raising agents, whereas atorvastatin, fluvastatin, and lovastatin increase HDL up to 9%. Treatment with statins results in a modest decrease in serum TAG of approximately 7% to 30%. In general, the larger the efficacy of statins in reducing LDL, the greater the associated effect on lowering the TAG.

Fish Oils

Fish oils contain a high concentration of polyunsaturated fatty acids (PUFAs) and have been shown to reduce plasma triglycerides up to 45%, although they may be associated with increased LDL levels. There is evidence suggesting that fish oils, more specifically the omega-3 PUFAs, provide beneficial cardiovascular effects [53]. Omega-3-acid ethyl esters are available as an adjunct to diet for the reduction of very high TAG levels (≥500 mg/dl) in adults. The mechanism of action is poorly defined but may involve the inhibition of acyl CoA:1,2-diacylglycerol acyltransferase and increased peroxisomal β-oxidation in the liver. A novel agent ethyl eicosapentaenoic acid (EPA), which is a semisynthetic derivative of omega-3 fatty acids, has been shown to significantly lower triglyceride levels in patients with very high triglyceride levels without significantly increasing LDL cholesterol levels [54].

New Treatment Options for Increasing HDL

Several new and exciting therapies for reducing HDL are currently undergoing intense investigation. Cholesteryl ester transfer protein (CETP) inhibition is the most promising new therapy and consists of inhibiting CETP, a plasma glycoprotein produced in the liver that circulates in the bloodstream bound to HDL that facilitates transfer of cholesterol esters between lipoproteins. CETP activity is potentially atherogenic and results in the net transfer of cholesterol esters from HDL to VLDL and LDL, thereby decreasing the concentration of HDL and increasing the concentration of LDL. Pharmacologically inhibiting CETP has been shown to increase the reverse cholesterol transport to the liver by increasing

HDL and enhancing the hepatic uptake of cholesterol via scavenger receptor B-1 (SRB-1) [55].

The clinical trials evaluating the CETP inhibitor torcetrapib demonstrated that while this drug was highly effective at increasing HDL, this was associated with increased risk of death and cardiovascular events. The preliminary results from the randomized DEFINE trial (Determining the Efficacy and Tolerability of Anacetrapib) showed that treatment with selective CETP inhibitor anacetrapib in 1,623 patients with CHD had a 36% decrease in LDL and 138% increase in HDL with no associated cardiovascular adverse events seen with previous CETP inhibitors [56]. The REVEAL HPS-3 TIMI-55 trial will include 30,000 CHD patients and will evaluate the effect of anacetrapib on clinical cardiovascular outcomes.

LIPOPROTEIN(A)

Lipoprotein(a) or Lp(a) is a lipoprotein similar to LDL in lipid and protein concentration but is composed of two protein particles, apolipoprotein (apo) B-100 and apolipoprotein(a) [57]. The precise role of Lp(a) in the pathogenesis and progression of atherosclerosis remains controversial [5], but potential mechanisms of Lp(a) include binding to proinflammatory oxidized phospholipids [58], decreased nitric oxide synthesis, increased leukocyte adhesion and smooth muscle proliferation, and inhibition of the fibrinolytic system. However, substantial uncertainty remains regarding the role of Lp(a) in clinical practice, although an elevated level might warrant more aggressive treatment in patients who have high-risk family histories but few other risk factors. Statins do not decrease Lp(a) levels, and statin therapy may increase in Lp(a) approximately 30%. Niacin currently is the only available lipid-lowering drug that significantly reduces the plasma levels of Lp(a).

HOMOCYSTEINE

An elevated level of homocysteine has been implicated as a risk factor for coronary atherosclerosis, although the precise pathophysiology behind this association remains undefined [5]. A large, randomized trial enrolling 3,749 patients (NORVIT trial) [59] showed that the combination of high-dose vitamin B_6 and folic acid reduced homocysteine levels by 28% but was associated with an increased the risk of stroke and MI. Thus, the current evidence does not support the routine treatment of elevated homocysteine levels in the general population to prevent cardiovascular events (*Grade B*).

FUTURE DIRECTIONS

Although the mean total cholesterol levels in adults in the United States have progressively declined, significant populations still have lipid levels that place them at higher risk for adverse cardiovascular events [60]. The increasing prevalence of obesity, metabolic syndrome, and diabetes mellitus mandates comprehensive therapeutic strategies for dealing with multiple lipid and metabolic disorders. The treatment of LDL cholesterol remains the cornerstone of therapy; however, therapeutic options for increasing HDL cholesterol and lowering triglycerides will continue to evolve rapidly and will be the major targets for future interventions. The accurate assessment of the patients at risk for the development and progression of ASCVD and the optimal goals for therapy will continue to be the major focus of basic research and clinical trials in the future.

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This large, randomized, placebo-controlled trial compared pravastatin (40 mg/d) with placebo in 4,159 patients (3,583 men and 576 women) with MI who had "average" cholesterol levels (mean total cholesterol, 209 mg/dl; mean LDL, 139 mg/dl). A 24% relative risk reduction occurred in the pravastatin group compared with placebo in fatal coronary event or nonfatal MI (10.2% vs.13.2%; 95% CI, 9%–36%; $p = 0.003$), less coronary bypass surgery (7.5% vs. 10%, $p = 0.005$), and less coronary angioplasty (8.3% vs. 10.5%; $p = 0.01$), and 31% relative risk reduction in stroke ($p = 0.03$).

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    In this study, lipoprotein subclass analyses were performed on frozen plasma samples from 241 participants in the PLAC-1 trial by using an automated NMR technique. Within treatment groups, CAD progression was most strongly related to the LDL particle number (placebo) and levels of small HDL (pravastatin). In logistic regression models that adjusted for chemically determined lipid levels and other covariates, a small LDL level of 30 mg/dl (median) or more was associated with a ninefold increased risk of CAD progression ($p < 0.01$) in the placebo group.

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reduced the incidence of a first major coronary event (fatal or nonfatal MI, unstable angina, or sudden cardiac death) (relative risk [RR], 0.63; 95% CI, 0.50–0.79; $p < 0.001$), MI (RR, 0.60; 95% CI, 0.43–0.83; $p = 0.002$), unstable angina (RR, 0.68; 95% CI, 0.49–0.95; $p = 0.02$), and coronary revascularization procedures (RR, 0.67; 95% CI, 0.52–0.85; $p = 0.001$).

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    This large, randomized, placebo-controlled trial evaluated the effects of simvastatin (40 mg/d) in 20,536 subjects (aged 40–80 years) with coronary disease, other occlusive arterial disease, or diabetes, irrespective of their baseline LDL level. All-cause mortality was significantly reduced (12.9% vs.14.7%; $p = 0.0003$) because of a highly significant 18% reduction in the coronary death rate (5.7% vs. 6.9%; $p = 0.0005$). A significant reduction in adverse events was found, even in those who presented with an initial LDL cholesterol below 116 mg/dl.

19. (1) **Cannon CP** et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 2004;350:1495–1504.

    This large, randomized trial enrolled 4,162 patients with an acute coronary syndrome within the preceding 10 days and compared treatment with pravastatin (40-mg/d standard therapy) with atorvastatin (80-mg/d intensive therapy). After a mean follow-up of 24 months, the median LDL achieved during treatment with pravastatin was 95 mg/dl compared with 62 mg/dl with the high-dose atorvastatin group ($p < 0.001$). A 16% relative risk reduction was noted in the rates of the primary end point (composite of death from any cause, MI, documented unstable angina requiring rehospitalization, coronary revascularization, and stroke) in the atorvastatin group compared with the pravastatin group (22.4% vs. 26.3%; 95% CI, 5%–26%; $p = 0.005$). The study did not meet the prespecified criterion for equivalence but did identify the superiority of the more intensive regimen.

20. (1) **LaRosa JC** et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med 2005;352:1425–1435.

    This was a large, randomized trial, which prospectively evaluated the efficacy and safety of lowering LDL cholesterol levels below 100 mg/dl in patients with stable CHD. The 10,001 subjects were randomly assigned to double-blind therapy and received 10 mg or 80 mg of atorvastatin per day. After a median follow-up of 4.9 years, the mean LDL levels were 77 mg/dl in the 80-mg atorvastatin treatment group, and 101 mg/dl in the 10-mg atorvastatin treatment group. The incidence of persistent elevations in liver aminotransferase levels was 0.2% in the low-dose group and 1.2% in the high-dose group ($p < 0.001$). The primary event (occurrence of a first major cardiovascular event, defined as death from CHD, nonfatal non-procedure-related MI, resuscitation after cardiac arrest, or fatal or nonfatal stroke) occurred in 8.7% receiving 80 mg of atorvastatin, as compared with 10.9% receiving 10 mg of atorvastatin (22% relative reduction in risk [hazard ratio, 0.78; 95 CI, 0.69–0.89; $p < 0.001$]). No difference was seen between the two treatment groups in overall mortality.

21. (4) **O'Keefe JH Jr** et al. Optimal low-density lipoprotein is 50 to 70 mg/dl: Lower is better and physiologically normal. J Am Coll Cardiol 2004;43:2142–2146.

    This article concisely reviews the recent randomized trial data supporting reduced atherosclerosis progression and CHD events with lowering LDL to less than 70 mg/dl. The authors emphasize that no major safety concerns have surfaced in studies that lowered LDL to this range of 50 to 70 mg/dl.

22. (2) **Hunninghake DB** et al. The efficacy of intensive dietary therapy alone or combined with lovastatin in outpatients with hypercholesterolemia. N Engl J Med 1993;328: 1213–1219.

    In this trial, 111 outpatients with moderate hypercholesterolemia were treated with the NCEP Step 2 diet (low in fat and cholesterol) and lovastatin (20 mg/d), both alone and together. The LDL level was reduced by a mean of 5% (95% confidence interval, 3%–7%) during the low-fat diet compared with the high-fat diet ($p < 0.001$). With lovastatin therapy as compared with placebo, the reduction was 27%, whereas the combination of diet and drug therapy resulted in a mean LDL reduction of 32%.

23. (1) **Baigent C** et al. Efficacy and safety of cholesterol-lowering treatment: Prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005;366:1267–1278.

This is a prospective meta-analysis of data from 90,056 individuals in 14 randomized trials involving statin therapy. A 12% proportional reduction in all-cause mortality occurred per mmol/l reduction in LDL cholesterol (rate ratio [RR] 0.88; 95% CI, 0.84–0.91; $p < 0.0001$), a 19% reduction in coronary mortality (0.81; 0.76–0.85; $p < 0.0001$), lower rates of MI or coronary death (0.77; 0.74–0.80; $p < 0.0001$), and lower rates of coronary revascularization (0.76; 0.73–0.80; $p < 0.0001$), and fatal or nonfatal stroke (0.83; 0.78–0.88; $p < 0.0001$). The proportional reduction in major vascular events differed significantly ($p < 0.0001$) according to the absolute reduction in LDL cholesterol achieved. These benefits were significant within the first year but were greater in subsequent years.

24. (1) **Schwartz GG** et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: The MIRACL study: A randomized controlled trial. JAMA 2001;285:1711–1718.

    This large, randomized, placebo-controlled trial enrolled 3,086 patients with an acute coronary syndrome to treatment with atorvastatin (80 mg/d) initiated within 24 to 96 hours. At 16 weeks follow-up, a reduction in adverse cardiac events was noted (death, nonfatal acute MI, cardiac arrest with resuscitation, or recurrent symptomatic myocardial ischemia with objective evidence and requiring emergency rehospitalization) in the atorvastatin group compared with placebo (14.8% vs. 17.4%, relative risk [RR], 0.84; 95% CI, 0.70–1.00; $p = 0.048$), which was driven mainly by recurrent symptomatic ischemia. In the atorvastatin group, the mean LDL declined from 124 mg/dl to 72 mg/dl; however, elevated liver transaminases (>3 times) were more common than in the placebo group (2.5% vs. 0.6%; $p < 0.001$).

25. (1) **de Lemos JA** et al. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: Phase Z of the A to Z trial. JAMA 2004;292:1307–1316.

    This large, randomized trial compared the early initiation of an intensive simvastatin regimen (40 mg/d for 1 month and then 80 mg/d) with delayed initiation of a less-intensive regimen (placebo for 4 months and then 20 mg/d) in 4,497 patients with an acute coronary syndrome. Although the primary end point was not achieved, the early initiation of an aggressive simvastatin regimen resulted in a favorable trend toward reduction of major cardiovascular events.

26. (1) **Colhoun HM** et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): Multicentre randomised placebo-controlled trial. Lancet 2004;364:685–696.

    This large, randomized, placebo-controlled trial evaluated the effectiveness of atorvastatin (10 mg/d) for primary prevention of major cardiovascular events in 2,838 patients with type 2 diabetes without high concentrations of LDL cholesterol. After a median follow-up of 3.9 years, a 37% relative risk reduction in cardiovascular events was seen in the atorvastatin group compared with placebo (95% CI, 0.52–0.17; $p = 0.001$).

27. (1) **Wanner C** et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. N Engl J Med 2005;353:238–248.

    This was a large, randomized, double-blind, placebo-controlled trial evaluating the effect of treatment with atorvastatin (20 mg/d) in 1,255 subjects with type 2 diabetes mellitus receiving hemodialysis. After a median follow-up of 4 years, no significant difference was found in the primary end point (composite of death from cardiac causes, nonfatal MI, and stroke) in the atorvastatin group compared with placebo (relative risk, 0.92; 95 CI, 0.77–1.10; $p = 0.37$). This failure of statins in reducing the risk of cardiac event rates may have related to the need for starting treatment earlier, the need for longer follow-up, the high risk of death from other causes in hemodialysis patients (such as electrolyte imbalances or infection), or the differences in the nature of atherosclerosis in hemodialysis patients. The ongoing Study of Heart and Renal Protection (SHARP) trial will study the benefit of combination therapy with simvastatin and ezetimibe compared with placebo in approximately 9,000 subjects with advanced kidney disease, and the Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA) will compare treatment with rosuvastatin with placebo in 2,700 hemodialysis patients and will help to clarify this issue in the future.

28. (1) **Shepherd J** et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): A randomised controlled trial. Lancet 2002;360:1623–1630.

    This randomized trial enrolled 5,804 elderly patients (70–82 years) with a history of or risk factors for vascular disease to pravastatin (40 mg/d; $n = 2,891$) or placebo. After a mean follow-up of 3.2 years, there was a reduction in the primary end point (composite of coronary death, nonfatal MI, and fatal or nonfatal stroke) in the pravastatin group compared with placebo (hazard ratio, 0.85; 95% CI, 0.74–0.97; $p = 0.014$).

29. (1) **Fellstrom B** et al.; AURORA study group. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. N Eng J Med 2009;360:1395–1407.

Large, randomized, double blind, placebo-controlled trial recruited patients with CKD on hemodialysis and randomized to rosuvastatin versus placebo. The trial demonstrated no statistically significant difference between the two groups for both the primary outcome, CHD mortality and the secondary outcome, all mortality.

30. (1) **Boigent C** et al, SHARP investigators. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of heart and renal protection): a randomized placebo-controlled trial. Lancet 2011;377:2181-2192.

    Randomized, controlled trial recruited 9,438 patients with CKD and no known CVD and randomized to simvastatin plus ezetimibe versus simvastatin. Patients were followed for 5 years, and ezetimibe treatment group found to have one-sixth fewer MIs, strokes, or major cardiovascular event.

31. (2) **Brown G** et al. Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B. N Engl J Med 1990;323:1289–1298.

    This angiographic trial enrolled 120 men with hypercholesterolemia treated with lovastatin (20 mg, b.i.d) and colestipol (10 g, t.i.d); niacin (1 g, four times a day), and colestipol (10 g, t.i.d.); or conventional therapy with placebo. Intensive lipid-lowering therapy reduced the frequency of progression of coronary lesions, increased the frequency of regression, and reduced the incidence of cardiovascular events.

32. (1) **Nissen SE** et al. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: A randomized controlled trial (REVERSAL). JAMA 2004;291:1071–1080.

    This study compared the effect of regimens designed to produce intensive lipid lowering or moderate lipid lowering on coronary artery atheroma burden and progression, intensive lipid-lowering treatment with atorvastatin (mean LDL, 79 mg/dl), and reduced progression of coronary atherosclerosis compared with pravastatin (mean LDL, 110 mg/dl). Compared with baseline values, patients treated with atorvastatin had no change in atheroma burden, whereas patients treated with pravastatin showed progression of coronary atherosclerosis.

33. (2) **Robinson JG** et al. Pleiotropic effects of statins: Benefit beyond cholesterol reduction? A meta-regression analysis. J Am Coll Cardiol 2005;46:1855–1862.

    This article reviewed the data from five diet, three bile acid sequestrant, one surgery, and ten statin trials, with 81,859 participants, and found that the regression lines for nonstatin and statin trials were similar and consistent with a one-to-one relation between LDL-C lowering and CHD and stroke reduction over 5 years of treatment.

34. (4) **Rosenson RS**. Current overview of statin-induced myopathy. Am J Med 2004;116:408–416.

    This article reviews the risk factors associated with statin-induced myopathy and emphasizes the pharmacokinetic properties of the various agents and the proper selection and identification of patients at risk for myotoxic effects.

35. (4) **Pasternak RC** et al. ACC/AHA/NHLBI Clinical advisory on the use and safety of statins. Circulation 2002;106:1024–1028.

    This consensus statement summarizes the recommendations concerning the various safety issues surrounding the proper utilization of statins in clinical medicine.

36. (4) **Brown WV**. Cholesterol absorption inhibitors: Defining new options in lipid management. Clin Cardiol 2003;26:259–264.

    This article reviews the pharmacokinetics and pharmacodynamics of ezetimibe and summarizes the results from available clinical trials.

37. (1) **Ballantyne CM** et al. Dose-comparison study of the combination of ezetimibe and simvastatin (Vytorin) versus atorvastatin in patients with hypercholesterolemia: The Vytorin Versus Atorvastatin (VYVA) study. Am Heart J 2005;149:464–473.

    This randomized study compared the combination of ezetimibe/simvastatin with atorvastatin across dose ranges in 1,902 patients and found that at each milligram-equivalent statin dose comparison, and averaged across doses, ezetimibe/simvastatin provided greater LDL reductions (47%–59%) than atorvastatin (36%–53%).

38. (1) **Kastelein J** et al.; ENHANCE investigators. Simvastatin with or without Ezetimibe in familial hypercholesterolemia. N Eng J Med 2008;358:1431–1443.

    This double-blind, randomized trial compared simvastatin and ezetimibe versus simvastatin in patients with familial hypercholesterolemia (median LDL 318). Study demonstrated no statistically significant difference between two groups in carotid intima-media thickness.

39. (1) **Watts GF** et al. Effects on coronary artery disease of lipid-lowering diet, or diet plus cholestyramine, in the St Thomas' Atherosclerosis Regression Study (STARS). Lancet 1992;339:563–569.

This trial assessed the efficacy of dietary reduction and diet and cholestyramine on angiographic end points in men with CHD90 and found that dietary change alone slowed overall progression and increased overall regression of coronary artery disease, and diet plus cholestyramine was additionally associated with a net increase in coronary lumen diameter.

40. (4) **Rosenson RS**. The rationale for combination therapy. Am J Cardiol 2002;90:2K–7K.

    This article reviews the rationale for the use of combination therapy in the treatment of dyslipidemia, highlighting management strategies emphasizing the use of combination therapy involving statins in conjunction with niacin, fibric acid derivatives, or bile acid resins or intestinal inhibitors of active cholesterol transport.

41. (1) **Taylor A** et al. Extended release niacin or ezetimibe and carotid intima-media thickness. N Eng J Med 2009;361:2113–2122.

    This prospective, randomized, parallel group study compared the effectiveness of extended-release niacin versus ezetimibe when combined with statin by measuring carotid intima-media thickness. Carotid ultrasonography was performed to determine the level of intima thickness, and after 14 months, there was a significant decrease in carotid intima-media thickness in the niacin treatment group. There was no change in the carotid intima-media thickness in the ezetimibe treatment group.

42. (4) **Levy DR, Pearson TA**. Combination niacin and statin therapy in primary and secondary prevention of cardiovascular disease. Clin Cardiol 2005;28:317–320.

    This article reviews the impact of lipid-modifying combination therapy with niacin plus a statin on achieving lipid goals and improving clinical outcomes.

43. (1) **Brown BG** et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. N Engl J Med 2001;345:1583–1592.

    This trial evaluated simvastatin–niacin and antioxidant–vitamin therapy, alone and together, for cardiovascular protection in 160 patients with coronary disease and low plasma levels of HDL. This study showed that simvastatin plus niacin provides marked clinical and angiographically measurable benefits.

44. (1) **Pauciullo P** et al. Efficacy and safety of a combination of fluvastatin and bezafibrate in patients with mixed hyperlipidaemia (FACT study). Atherosclerosis 2000;150: 429–436.

    This randomized trial assessed the effect of fluvastatin (40 mg), bezafibrate (400 mg), fluvastatin (20 mg) + bezafibrate (400 mg), or fluvastatin (40 mg) + bezafibrate (400 mg) for 24 weeks in 333 patients with CAD and mixed hyperlipidemia. Bezafibrate alone and fluvastatin + bezafibrate combinations resulted in greater increases in HDL and decreases in TAG compared with fluvastatin alone ($p < 0.001$).

45. (1) **Hokanson JE, Austin MA**. Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: A meta-analysis of population-based prospective studies. J Cardiovasc Risk 1996;3:213–219.

    This meta-analysis evaluated the magnitude of the association between triglyceride and cardiovascular disease in the general population and found that triglyceride is a statistically significant risk factor in men (RR, 1.14; 95% CI, 1.05–1.28) and in women (RR, 1.37; 95% CI, 1.13–1.66) for cardiovascular disease, independent of HDL cholesterol.

46. (2) **Rubins HB** et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol: Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. N Engl J Med 1999;341:410–418.

    This large, randomized trial in 2,531 men with CHD and hypercholesterolemia with low HDL (HDL ≤40 mg/dl and an LDL ≤140 mg/dl) compared gemfibrozil (1,200 mg/d) and placebo. After a median follow-up of 5.1 years, a 22% relative risk reduction in the gemfibrozil group was found in the primary end point (nonfatal MI or coronary death) (17.3% vs. 21.7%; 95% CI, 7%–35%; $p = 0.006$).

47. (2) **Gordon T** et al. High density lipoprotein as a protective factor against coronary heart disease: The Framingham Study. Am J Med 1977;62:707–714.

    This trial evaluated the association of lipoprotein values, including fasting TAG, HDL, and LDL in 2,815 men and women (ages 49–82) on cardiac event rates and found that the major potent lipid risk factor was HDL, which had an inverse association with the incidence of CHD ($p < 0.001$).

48. (2) **Gordon DJ** et al. High-density lipoprotein cholesterol and cardiovascular disease: Four prospective American studies. Circulation 1989;79:8–15.

    This study analyzed the data from four prospective large trials and found that a 1-mg/dl increase in HDL was associated with a significant CHD risk reduction of 2% in men and 3% in women.

49. (4) **Shah PK** et al. Exploiting the vascular protective effects of high-density lipoprotein and its apolipoproteins: An idea whose time for testing is coming, part II. Circulation 2001;104:2498–2502.

This article reviews the pathophysiology and mechanisms behind the potential vascular protective effects of HDL.

50. (1) **Canner PL** et al. Fifteen year mortality in Coronary Drug Project patients: Long-term benefit with niacin. J Am Coll Cardiol 1986;8:1245–1255.

This trial evaluated the efficacy and safety of five lipid-lowering drugs in 8,341 men with established CHD. With a mean follow-up of 15 years, nearly 9 years after termination of the trial, mortality from all causes in each of the drug groups, except for niacin, was similar to that in the placebo group. Mortality in the niacin group was 11% lower than that in the placebo group (52% vs. 58.2%; $p = 0.0004$).

51. (1) **Huttunen JK** et al. The Helsinki Heart Study: Central findings and clinical implications. Ann Med 1991;23:155–159.

This article elaborates on the main findings and clinical implications of the Helsinki Heart Study, which was a controlled primary prevention evaluating the efficacy of gemfibrozil in lowering LDL, raising HDL, and reducing subsequent adverse cardiac events.

52. (1) **Keech A** et al. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): Randomised controlled trial. Lancet 2005;366:1849–1861.

This large, randomized, placebo-controlled trial evaluated the effect of fenofibrate on cardiovascular disease events in 9,795 patients (aged 50–75 years) with type 2 diabetes mellitus. After 5 years, no difference was found in overall mortality (6.6% in the placebo group and 7.3% in the fenofibrate group [$p = 0.18$]). Although fenofibrate did not significantly reduce the risk of the primary outcome of coronary events, it did reduce total cardiovascular events, mainly because of fewer nonfatal MIs and revascularizations (RR, 0.79; CI, 0.68–0.93; $p = 0.003$). The higher rate of starting statin therapy in patients assigned to placebo may have attenuated a larger treatment benefit.

53. (1) **Kromhout D** et al. n-3 fatty acids and cardiovascular disease after myocardial infarction. N Eng J Med 2010;363:2015–2026.

In this multicenter, placebo-controlled trial, 4,837 patients who had undergone an MI were randomized to receive one of four margarines made with omega-3 fatty acid. On average, patients consumed 2 g of omega-3 fatty acid per day but had no change in the rate of cardiovascular events.

54. (1) Efficacy and Safety of AMR101 (Ethyl Icosapentate) in Patients with Fasting Triglyceride Levels >500 and <2000 mg/dL (MARINE). Clinical Trials.gov

Phase III clinical trial comparing AMR101 versus placebo to determine triglyceride-lowering effect

55. (4) **Barter PJ, Kastelein JJ**. Targeting cholesteryl ester transfer protein for the prevention and management of cardiovascular disease. J Am Coll Cardiol 2006;47:492–499.

This review article summarizes the current basic science and clinical data on cholesteryl ester transfer protein (CETP) inhibitors (JTT-705 and torcetrapib) and their role in the treatment of low HDL.

56. (1) **Cannon CP** et al.; DEFINE group. Safety of anacetrapib in patients with or at high risk for coronary heart disease. N Eng J Med 2010;363:2406–2415.

This phase III clinical trial investigated the safety of anacetrapib, a CETP inhibitor, to decrease LDL and increase HDL. Patients were recruited to receive anacetrapib versus placebo and found to have 39.8% decrease in LDL and 138.1% increase in HDL. The medication was found to be safe over the treatment period of 24 weeks.

57. (4) **Deb A, Caplice NM**. Lipoprotein(a): New insights into mechanisms of atherogenesis and thrombosis. Clin Cardiol 2004;27:258–264.

This review discusses the structure of Lp(a) in relation to its biochemical actions, summarizes the current data on various pathophysiologic mechanisms of Lp(a)-induced vascular disease, and the role of cell and tissue-specific effects in promoting atherosclerosis.

58. (2) **Tsimikas S** et al. Oxidized phospholipids, Lp(a) lipoprotein, and coronary artery disease. N Engl J Med 2005;353:46–57.

This study measured levels of oxidized LDL and Lp(a) lipoprotein in 504 patients immediately before coronary angiography and found that circulating levels of oxidized LDL are strongly associated with angiographically documented coronary artery disease, particularly in patients 60 years of age or younger. These data suggest that the atherogenicity of Lp(a) lipoprotein may be mediated in part by associated proinflammatory oxidized phospholipids.

59. (1) Preliminary Results of the Norwegian Vitamin Trial (NORVIT) presented at the European Society of Cardiology Congress in Stockholm, Sweden; September 2005.

This large, randomized, placebo-controlled trial evaluated various combinations of high-dose vitamin B_6 and folic acid in 3,749 MI survivors. The results revealed that the combination of vitamin B_6 and folic acid, as well as folic acid alone, effectively lowered homocysteine levels by 28%, without any improvement in clinical outcomes. The risk of stroke and MI was 18% in the placebo group, which was similar to both the folic acid–only group and the vitamin B_6–only group. By contrast, in the combination group, 23% of patients had a fatal or nonfatal stroke or MI, a statistically significant absolute increase of 5%, compared with the other treatment arms ($p = 0.029$).

60. (3) **Arnett DK** et al. Twenty-year trends in serum cholesterol, hypercholesterolemia, and cholesterol medication use: The Minnesota Heart Survey, 1980–1982 to 2000–2002. Circulation 2005;112:3884–3891.

This study examined the 20-year trends in cholesterol, hypercholesterolemia, lipid-lowering drug use, and cholesterol awareness, treatment, and control from Minnesota Heart Survey (MHS). The results showed that although hypercholesterolemia prevalence continued to fall, significant population segments still have cholesterol concentrations near or at the level of increased risk.

8

Obesity and Nutrition

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DEFINITION

Obesity is a chronic disease diagnosed when an adult person has a body mass index (BMI) of 30 to 34.9 (class I), 35 to 39.9 (class II), more than 40 (class III, "extreme obesity"), more than 50 (class IV, "super obesity"), or more than 60 kg/m^2 ("super-super obesity"). BMI is not a direct measure of adiposity but rather a derived value correlated with total body fat and risk for certain complications. BMI is calculated as the weight in kilograms, divided by the height in meters squared. Alternatively, one can calculate the weight in pounds, divide by the height in inches squared, and multiply by 703. Risks for cardiovascular disease (CVD), type 2 diabetes (T2DM), and hypertension are further defined by subgrouping overweight BMI (25–29.9 kg/m^2) or obese BMI categories into those with increased abdominal obesity by waist circumference: more than 102 cm (40 inches) for men and 88 cm (35 inches) for women or by waist-to-hip ratio: more than 0.9 for men and more than 0.85 for women. However, optimal metrics for risk stratification have not been determined. For instance, in a German population, waist-to-height ratio was more predictive of CVD risk and mortality than waist-to-hip ratio, waist circumference, or BMI [1]. Additionally, among patients considered for Roux-en-Y gastric bypass (RGB) bariatric surgery, the obesity surgery mortality risk score (based on BMI ≥50 kg/m^2, male gender, hypertension, risk for pulmonary embolism, and age ≥45 years) has been shown to predict postoperative mortality [2]. In pediatric and adolescent persons, BMI percentiles for ages 2 to 17 years are used. "Overweight" persons are those between the 85th and 95th percentiles, and "obese" persons are above the 95th percentile [3]. Obesity in youths is defined as BMI of 95th percentile or BMI of 30 kg/m^2, whichever is lower. Different protocols for intervention are recommended based on these categories. For children less than 2 years of age, BMI normative values are not available.

EPIDEMIOLOGY

More than 1.7 billion persons worldwide are overweight or obese [4]. The prevalence of overweight or obesity among United States adults in 2007 to 2008 was 68%; obesity, 33.8%; and class III obesity, 5.7%, with women generally having a higher prevalence of obesity compared with men [5]. The prevalence of obesity in children or adolescents during the same time period was 16.9% [6] and 17% overweight [7]. In 2006 to 2008, non-Hispanic blacks had the greatest prevalence of obesity (35.7%), followed by Hispanics (28.7%), and non-Hispanic whites (23.7%) [8]. The differences were greater among women than men. The 30-year risks of being overweight are more than 91% for men and 73% for women, of being obese are more than 47% for men and 38% for women, and of having class III obesity or more are more than 4% for men and 6% for women [9]. Increasing BMI is associated with the prevalence of T2DM, heart disease, hypertension, dyslipidemia, asthma, arthritis, certain cancers (colon, cervix, breast, prostate, and lung), venous thromboembolic disease, sleep apnea, and poor general health [10,11]. In the 2010 study by Berrington [12], both overweight and obesity are associated with increased all-cause mortality.

Irrespective of BMI, the accumulation of fat in the abdomen, pancreas, liver, and muscle is strongly associated with the metabolic complications of obesity [13], hypertension [14], and CVD [15]. Depending on the definition used, visceral obesity is part of the "metabolic" or "insulin-resistance" syndrome, along with hypertension, impaired glucose regulation, dyslipidemia, and other biomarkers for prothrombotic and proinflammatory states [16]. Metabolic syndrome is a univariate predictor of coronary heart disease (odds ratio, 2.07) [17]. The INTERHEART study was the first large multiethnic study to show that metabolic syndrome is a risk for MI, and the risk of MI increased as more component factors were present [18].

Metabolic syndrome also predicts development of T2DM, and weight reduction of 3 to 6 kg by lifestyle change or medication (orlistat or metformin) reduces the risk for T2DM [19–21]. In a recent study of over 32,024 mostly Caucasian Americans, 13.1% of women and 30.5% of men had metabolic syndrome defined by NCEP ATIII criteria. However, the definition, implications, and even semantics of this syndrome have been challenged [22,23].

ETIOLOGY

Obesity is the result of certain genetic and environmental factors that result in positive energy balance (calorie consumption > energy expenditure). Heritability accounts for 30% to 70% of the variation in body mass within a population, but consistently replicated common genetic variants have not been associated with common obesity [24–26]. Genetic factors determine set points for appetite, intermediary metabolism, and physical activity behavior. Environmental factors that produce a state of energy surfeit consist of (1) prenatal factors; (2) availability of inexpensive, palatable, energy-dense foods; (3) large portion sizes; (4) social, economic, ethnic, and cultural pressures to overconsume food; (5) media advertising; and (6) sedentary lifestyle [27]. It has been proposed that increased consumption of energy-dense foods (relatively low in water content [dry], high in fat content, and particularly found in "fast foods") is a major contributor to the obesity epidemic. One theory suggests that humans have a weak ability to recognize high-energy-density foods and to downregulate the bulk of food ingested to avoid consumption of excess calories [28]. However, a critical review of the data concluded that a causal relation has not been clearly demonstrated [29]. Similarly, high-fat diets have not been shown to cause excess body fat in the general population [30], although genetically susceptible individuals may exist [31].

Interestingly, breakfast consumption, especially those including a ready-to-eat (RTE) cereal, has been shown to correlate with lower BMI and lower risk of obesity in women, as compared with skipping breakfast [32]. Ruxton et al. [33] asserted that a breakfast meal high in fiber and low in fat represents a beneficial nutritional profile and decreased risk for obesity, but longitudinal studies are required to confirm this association.

PATHOPHYSIOLOGY

Appetite centers in the paraventricular nucleus, arcuate nucleus, and lateral hypothalamus play a central role in allowing overconsumption of calories. Ghrelin is orexigenic (stimulates appetite), is produced by the stomach, and has a dominant role over leptin, which is anorexigenic (inhibits appetite) and is produced by adipose cells. In the arcuate nucleus, adenosine monophosphate–activated protein kinase, agouti-related protein, neuropeptide Y, γ-aminobutyric acid, and galanin inhibit the satiety centers of the arcuate and paraventricular nuclei and stimulate the feeding center of the lateral hypothalamus, which also decreases energy expenditure. Peptides in the arcuate nucleus satiety center include proopiomelanocortin (POMC), α-melanocyte–stimulating hormone, cocaine- and amphetamine-related transcript, and neurotensin. Gut hormones, such as insulin, glucagon-like peptide 1 (GLP-1), peptide YY, and cholecystokinin, inhibit the feeding centers, activate the satiety centers, and increase energy expenditure. Polymorphisms that affect secretion or signal transduction of any of these pathways can influence the body composition set point. In addition, recent studies have implicated sleep disturbance in the pathophysiology of obesity. Brondel et al. [34] found that one night of reduced sleep increased food intake greater than physical activity–related energy expenditure in healthy men. At least one randomized study is underway to determine if extension of sleep duration affects BMI [35].

Once environmental factors exploit a genetically determined predisposition in body composition that creates obesity, an inflammatory state ensues. Adipokines (interleukin-6, tumor necrosis factor-α, leptin, and adiponectin) are products from adipose tissue that contribute to this inflammatory state with obesity. Hyperinsulinemia, which leads to decreased cardioprotection, is also associated with obesity and a proinflammatory state [36]. Thus, pathogenic adipose tissue, or adiposopathy, appears to play an important role in the development of obesity.

TREATMENT

The initial goal of therapy is to identify and treat associated CVD risk factors (high blood pressure, elevated glucose, dyslipidemia) and to prevent further weight gain. Then a realistic goal for weight loss should be determined. In general, an initial goal of 10% weight loss over a 6-month period with maintenance of lean body mass is feasible and reduces risk. Typically, faster weight loss occurs with diuresis during the first 2 weeks, followed by slower weight loss. By 6 months, weight loss plateaus, and patients may become discouraged. Patients should be reminded of the metabolic changes occurring with weight loss and the need for a maintenance program. Weight loss by as little as 3.8% in 2 years with dietary intervention was associated with salutary effects on cardiovascular parameters, and partial weight regain diminished these effects [37]. Although some observational studies have demonstrated an association of weight loss with mortality, the randomized ADAPT study demonstrated that "intentional" weight loss of overweight/obese (BMI > 34) older (median age 69 years) adults was not associated with increased risk for mortality and may even decrease the mortality risk [38].

Therapeutic Lifestyle Changes

The nonpharmacologic and nonsurgical management of obesity involves behavioral modification, healthy eating, and increased physical activity. This should be first-line therapy for obesity and continued throughout a person's life not only to enhance other therapies but also promote general health. In a pragmatic PRCT, intensive medical therapy (900 kcal liquid diet for up to 12 weeks, group behavioral counseling, structured diet, and choice of pharmacotherapy) of adults over 20 years with a BMI of 40 kg/m^2 or higher was associated with significant amounts of weight loss [39]. In obese adolescents, modest lifestyle–only changes are associated with a redistribution of body composition, improved insulin sensitivity, and decreased markers of inflammation [40].

Behavioral

Behavioral therapy is an essential requirement for all weight management interventions. Patients learn how to overcome obstacles and improve long-term adherence to lifestyle changes through behavioral therapy. Strategies include healthy eating, increased physical activity (though a recent study indicated that resistance training alone has little effect, if any, on the psychosocial profile [41]), recognizing unhealthy lifestyle patterns, self-monitoring (keeping logs), stress reduction, stimulus identification and control, setting goals and offering rewards, problem solving, and social support. Behavioral therapy can induce a 5% to 10% weight loss and is more effective than a very-low-calorie diet alone [42–44].

Commercially available weight loss programs, involving portion control and education, can reduce CVD risk [45], and larger clinical trials are currently underway to confirm these findings [46]. In the PREMIER trial, lifestyle interventions were found to reduce 10-year CVD risk by 12% to 14% [47]. These programs need to be culturally sensitive in order to be effective in different patient populations [48]. Participation in group settings in the workplace has been shown to be effective [49]. Incorporation of self-determination principles in behavioral therapy is also important [50]. In overweight/obese postmenopausal women, restrictive messages to limit high-fat foods induced greater weight loss than nonrestrictive messages to include fresh fruits and vegetables [51].

In adolescents with a mean BMI of 37.6 ± 3.3 kg/m^2, behavioral therapy favorably redistributed body composition in the absence of weight loss while also improving insulin sensitivity and reversing the inflammatory state [40]. It is interesting that there is a difference between "liking" a food and "wanting" to eat that food; moreover, the pattern of this disparity varies with a patient's BMI [52]. For instance, consuming high-energy-density snack foods is not associated with decreased intake of that snack over time in obese patients, even though "liking" that food reportedly decreases [52]. In a meta-analysis of randomized studies of children, behavioral family-based treatment led to sustained weight loss [53]. Even a simple reduction in television viewing by 50% over a 3-week period of time can be associated with significant increases in energy expenditure without increases in energy intake [54].

Other benefits of behavioral therapy include improved biomarkers of vascular inflammation [55,56] and improvement in the weight loss response to pharmacotherapy [42,57,58]. In a randomized trial of 91 community members, use of computer-assisted dieting interventions were found to be associated with initial weight loss, but self-management training was needed for support maintenance [59]. Education about nutrition facts labels has also been associated with reduced energy intake [60]. Brochures and active education had comparable beneficial effects on the nutritional habits of obese pregnant women [61].

Weight gain can be expected with discontinuation of behavioral therapy. Sequential behavioral therapy for weight control after a program for smoking cessation may have superior results compared with concurrent weight control and smoking cessation interventions [62].

Healthy Eating and Nutrition

Patients with obesity should be encouraged to restrict calories while following basic principles of healthy eating. For most patients, reducing intake by 500 kcal/d leads to a 0.5- to 1-lb weight loss per week and is associated with no increased risk. Low-energy diets can also improve endothelial function [63] and obesity-related comorbidity symptoms, such as obstructive sleep apnea [64]. Diets should be low in saturated fat (<10% total calories) and dietary cholesterol (<300 mg/d) with minimal *trans* fatty acids and the majority of dietary fat consumed as monounsaturated fatty acids (MUFA) to decrease the risk of atherosclerosis [65]. However, the type of dietary fat consumed does not appear to affect postingestion satiety or energy intake [66]. The incorporation of larger portions of low-energy-dense foods, such as fruits and vegetables, provides essential fiber and phytonutrients while maintaining satiety and restricting energy intake [67]. Including a whole grain RTE oat cereal as part of a dietary program was associated with improved waist circumference and fasting lipid levels [68]. The consumption of caloric beverages with a standard meal is best avoided, as they do not increase satiety and only increase calories consumed [69].

The optimal macronutrient distribution for weight loss has been frequently debated and remains controversial. It is most likely that one approach will not suit all patients. Four randomized controlled studies demonstrated greater weight loss at 6 months, but not by 1 year, with low-carbohydrate diets [70–74]. A plant-based (vegan), low-fat diet, without any prescribed limits on portion size or energy intake, was associated with greater weight loss (−5.8 kg vs. −3.8 kg) compared with a control diet [75]. In a meta-analysis, low-fat diets were not found to be superior to calorie-restricted diets [76]. TCF7L2 is a necessary transcription factor for proglucagon gene expression and GLP-1 synthesis, which is higher after ingesting fat than carbohydrate. Obesity modifies the association of TCF7L2 with T2DM. In a PRCT conducted by Grau et al. [77], patients on average experienced similar effects of a −600 kcal/d hypoenergetic high-fat (40%–45% energy), compared to those on a low-fat (20%–25% energy), diet on body weight/composition and insulin resistance. However, those patients who were homozygous for the *TCF7L2* rs7903146 *T*-risk allele had less of these effects with the high-fat diet [77]. This observation illustrates the emergent science of nutrient–gene interactions relevant to obesity research.

Some studies suggest that diets higher in protein (25%–30%) may increase satiety and result in lower caloric intake in a free-living environment [78,79]. The mechanism for the satiating effect of dietary protein is unclear and not related to postprandial ghrelin secretion, as previously thought [80]. One study showed a greater decrease in triglycerides and reduced fat mass with a high-protein, low-fat diet relative to a conventional high-carbohydrate, low-fat diet, but the total weight loss was equivalent after 12 weeks [81]. Supplementation with whey protein (27 g PO b.i.d. × 12 weeks) was associated with improved fasting lipid and insulin levels in overweight/obese patients [82].

High-protein diets deliver a marked acid load to the kidney and thereby increase the risk for bone loss and kidney stones [83,84], although high-dose calcium supplementation during short-term calorie restriction can attenuate bone resorption [85]. High protein consumption can also accelerate chronic kidney disease (CKD) and should be avoided in patients with baseline elevated creatinine and used

with caution in patients at high risk for CKD, such as those with diabetes or hypertension [86]. Nevertheless, a recent PRCT of 68 obese patients with normal renal function at baseline failed to demonstrate any adverse effect on renal function of a very-low (4%) carbohydrate diet with 35% protein [87].

Weight loss (2.1–3.3 kg over a 1-year period) was comparable among various commercially available diets: Atkins (carbohydrate restriction), Zone (macronutrient balance), Weight Watchers (calorie restriction), and Ornish (fat restriction); successful weight loss was associated with adherence and cardiac risk factor reduction [88]. However, in a more recent study by Foster et al. [89], a low-carbohydrate diet (20 g/d) with low-glycemic-index foods and unlimited fat and protein was associated with higher HDL cholesterol levels at 2 years compared with a low-fat (≤ 30 g/d), low-energy (1,200–1,800 kcal/d) diet. All patients in the study received behavioral therapy, and both groups demonstrated weight loss (7%) at 2 years [89]. In addition, low-carbohydrate diets may have detrimental effects on vascular function and CVD risk [90,91].

Very-low-calorie diets (VLCD; <800 kcal/d) or "protein-supplemented modified fasts" and low-calorie diets (LCD; 800–1,500 kcal/d) are associated with comparable rates of weight loss, although more weight is lost initially with VLCDs. In a large, multicenter study [92] involving 1,389 patients followed up for at least 1 year on a VLCD providing 600 to 800 calories per day, mean weight loss was −6.9 ± 2.6 kg at 1 month, −12.3 ± 5.3 kg at 3 months, and −13.1 ± 8.0 kg at 12 months. The weight loss was primarily fat mass, as determined by bioimpedance analysis [92]. VLCDs require protein sources of high nutritional value and supplementation of vitamins and micronutrients, including sodium, potassium, calcium, iron, and magnesium. VLCDs are safest when monitored by a physician as part of a comprehensive weight reduction program. VLCDs are contraindicated in pregnancy and lactation, major psychiatric disease, severe systemic disease, and type 1 diabetes.

Another popular strategy in obesity treatment is the use of commercial meal replacements (liquids or bars). Meal replacements serve as both a nutritional and a behavioral strategy, as they provide calorie- and portion-controlled meals, generally fortified with vitamins and minerals, and they eliminate the need to make food choices. They are typically used to replace one or two meals daily. A recent PRCT of 80 obese patients demonstrated improved weight loss, body composition, and biochemical/clinical outcomes with a meal replacement program compared with a self-selected, food-based meal plan [93]. A meta-analysis of six controlled trials found that subjects on a diet plan that included liquid meal replacements lost 2.54 kg more at 3 months and 2.44 kg more at 1 year than did those on a reduced-energy food-based plan [94].

The risk for metabolic bone disease with diets that promote weight loss can be further increased by a concomitant vitamin D deficiency. 25-hydroxyvitamin D levels have been shown to correlate inversely with the percentage of body fat [95]. Prevalence rates for vitamin D deficiency (25-hydroxyvitamin D <16 ng/ml) up to 62% have been demonstrated in patients with a BMI greater than or equal to 40 kg/m^2 [96]. This is thought to be due to sequestration of 25-hydroxyvitamin D in fat, possibly in conjunction with reduced sun exposure. Consideration should be given to the need for calcium and vitamin D supplementation while dieting and, depending on the degree of calorie restriction, other micronutrients to prevent deficiencies.

Lastly, the routine use of dietary supplements in the management of obesity is not supported by strong evidence. Dietary supplements purported to induce weight loss, including bitter orange (*Citrus aurantium*), chromium picolinate, linoleic acid, chitosan, calcium, *Garcinia cambogia*, glucomannan, guar gum, β-hydroxymethylbutyrate, pyruvate, yerba mate, and yohimbe, show little

evidence of benefit [97]. Ephedra (ma-huang) demonstrated short-term efficacy, but its sale has been prohibited in the United States since 2004 because of an unacceptable risk of myocardial infarction, stroke, seizures, and death.

Functional foods that may facilitate weight loss and decrease oxidative stress are generally plant based and high in fiber and polyphenols. For example, consumption of a blueberry beverage, equivalent to 350 g of fresh blueberries, daily for 8 weeks in a PRCT improved CVD risk factors (blood pressure, oxidized LDL cholesterol, and markers of lipid peroxidation) in patients with metabolic syndrome [98]. In a prospective 12-week parallel-arm randomized controlled trial (N = 81), adding a low-sodium vegetable juice was associated with increased weight loss while also increasing the total amount of daily vegetable servings [99]. A diet replete in pulses (beans, lentils, chickpeas, and yellow peas) is associated with decreased risk for overweight/obesity by epidemiologic studies [100,101] but not due to the immediate (postprandial 120 minutes) effects on satiety [102].

Physical Activity

All patients must be encouraged to participate in daily physical activity, including a minimum of 30 minutes of exercise every day, or on most days of the week [103]. Additional physical activity may be necessary to increase energy expenditure in overweight or obese individuals to lose weight. Weight loss induced by physical activity each day, without calorie restriction, is at least as effective than calorie restriction–induced weight loss with respect to truncal obesity, insulin resistance, and CVD risk factors [104,105]. The loss of greater than 5% to 7% body weight in obese subjects can be associated with significant salutary effects on inflammatory markers, but moderate exercise alone (supervised aerobics, three times a week, 60–75 minutes and expenditure of 500–600 kcal per session) for 12 weeks does not have this effect [106]. When progressive resistance training is added to a weight loss program, there are significant improvements in CVD risk factors despite a drop in adiponectin, a cytokine from visceral fat generally associated with antidiabetic, anti-inflammatory, and antiatherogenic properties [107]. Thus, the complex nature of interactions among diet, physical activity, and adipose tissue pathophysiology remain to be clarified.

Over a period of 8 months, high-quantity and vigorous-intensity exercise (20 miles jogging per week) can decrease mean body mass by 3.5 kg and mean fat mass by 4.9 kg (with an increase in lean body mass of 1.4 kg), compared with low-amount and moderate-intensity exercise (12 miles walking per week, equivalent to 30 minutes a day), which can decrease mean body mass by 1.3 kg and mean fat mass by 2.0 kg (with an increase in lean body mass of 0.7 kg) [108]. When coupled with dietary advice, lifestyle changes including physical activity can result in weight reductions of 4.5 kg by 1 year and 3.5 kg by 3 years [109]. Greater amounts of exercise, with an energy expenditure goal of 2,500 kcal/wk, produce weight losses at 6, 12, and 18 months of 9.0, 8.5, and 6.7 kg compared with less exercise with an energy expenditure goal of 1,000 kcal/wk, producing weight losses of 8.1, 6.1, and 4.1 kg, respectively [110]. In sedentary women who increased physical activity and adhered to a 1,200- to 1,500-calorie, 20% to 30% fat diet, less than 150 min/wk exercise resulted in 4.7% weight loss; 150 to 200 min/wk, in 9.5%; and more than 200 min/wk, 13.6% [111]. When exercise counseling by a physiotherapist was evaluated along with nutritional counseling, patients decreased waist circumference but body weight was unchanged compared with nutritional counseling alone [112]. In a PRCT involving 83 patients with T2DM, the addition of a supervised resistance exercise training program to a high-protein diet (carbohydrate/protein/fat 43:33:22) significantly improved body composition, weight loss, and CVD risk factors [113]. Erdmann et al. [114],

studied the effects of carbohydrate- and protein-rich meals on exercise-induced lipolysis in 20 obese patients and concluded that carbohydrates should not be ingested immediately (within 2 hours) of exercise in order to optimize lipolysis. Ingesting a protein-rich meal can suppress hunger (the "empty stomach" feeling) and is a good alternative [114].

PHARMACOTHERAPY

Antiobesity medications are indicated in those patients for whom therapeutic lifestyle changes have failed and who have a BMI of 27 kg/m^2 or more (with comorbidities) or 30 kg/m^2 or more (without comorbidities). The amount of weight loss anticipated from antiobesity medications is 5% to 10% of body weight, but this has still been associated with CVD and T2DM risk reduction.

Orlistat

Orlistat is currently the only available weight loss agent FDA approved for long-term use. It is indicated for obesity management including weight loss and weight maintenance in patients with BMI greater than or equal to 30 or greater than or equal to 27 with other risk factors. Orlistat (Xenical, Alli) is an intestinal lipase inhibitor, which decreases the absorption of fat. Based on a meta-analysis of 50 studies, the pooled mean increased weight loss for orlistat (120 mg PO, t.i.d) and lifestyle changes, compared with placebo, was 2.59 kg at 6 months and 2.89 kg at 12 months [115]. A Cochrane review determined that sufficient evidence existed for orlistat for statistically significant weight loss for at least 1 year [116]. Orlistat plus lifestyle changes can decrease the risk for T2DM in patients with impaired glucose tolerance [21], and the drug now has an FDA-approved indication for diabetes prevention. Adverse effects include oily spotting, flatus with discharge, fecal urgency, and loose stools. Vitamin supplementation at night is recommended because of possible malabsorption of fat-soluble vitamins (A, D, E, and K). Concomitant use of fiber or psyllium can reduce these adverse effects [117]. The drug is dosed before each meal. A diet containing 30% fat is optimal to provide efficacy while minimizing adverse effects. The prescription drug is marketed as Xenical at 120 mg and over-the-counter as Alli in a reduced 60-mg dose. Orlistat is contraindicated in pregnancy, malabsorptive conditions, cholestasis, or known hypersensitivity.

Phentermine

Phentermine (Adipex-P, generic) is indicated for short term treatment of obesity (usually up to 12 weeks). It is a norepinephrine-releasing (amphetamine-like) agent that is effective as an appetite suppressant without producing euphoria. It is dosed once daily as a 37.5-mg tablet or capsule. With intermittent or continuous use, it results in a 5% to 15% weight loss. Adverse effects include agitation, anxiety, insomnia, tachycardia, and headaches. It should not be used in patients taking an MAO inhibitor. Phentermine should be used with great caution in patients at high risk for CVD.

Diethylpropion

Diethylpropion (Tenuate) is another amphetamine-like agent. The controlled-release formulation is dosed as 75-mg tablet once daily or immediate release 25 μg before each meal. Adverse effects may include dry mouth, restlessness, anxiety, dizziness, tremors, upset stomach, and increased urination. This drug has been approved for short-term use (a few weeks) since 1959 but has not been extensively studied.

History

Many previously available weight loss agents have been withdrawn from the market due to safety concerns. Fenfluramine, a previously widely prescribed serotonin-releasing agent, was withdrawn from the market in 1997 due to

increased risk of valvular heart disease. This drug had been particularly effective when used in combination with phentermine (Phen-Fen). Phenylpropanolamine, a norepinephrine releasing agent, was withdrawn from the market due to increased risk of stroke. Sibutramine (Meridia), an appetite suppressant with combined norepinephrine and serotonin reuptake inhibition, previously approved for long-term use for weight loss and weight maintenance, was withdrawn from the market in 2010 due to increased risk of nonfatal myocardial infarction and nonfatal stroke [118]. The cannabinoid-1 receptor blocker, rimonabant (Acomplia), previously available in Europe, was withdrawn from the European market in 2008 due to increased risk of suicidality and depression. Since then, development of other cannabinoid receptor antagonists has been suspended.

FUTURE DIRECTIONS

The anticonvulsant medication topiramate (25–600 mg daily) results in decreased food intake and is associated with a 6% to 17% weight loss after 14 to 60 weeks of use [119–122]. Topiramate may be most effective for those patients with obesity and binge-eating disorder [122,123]. Adverse effects include paresthesia, cognitive changes, depression, and nervousness. Qnexa (VIVUS, Inc.), a combination of phentermine and topiramate, has thus far failed to gain FDA approval.

The antiepileptic agent zonisamide has also been associated with weight loss in overweight patients [124]. In a randomized double-blind trial of 60 patients treated with zonisamide 400–600 mg versus placebo, subjects lost an average to 9.2 kg versus 1.5 kg in the placebo group at 32 weeks [125]. All subjects were counseled to reduce intake by 500 kcal/d, adhere to a healthy diet, and encouraged to be physically active. Zonisamide is also being studied in combination with bupropion for weight loss.

Lorcaserin (Arena Pharmaceuticals) is a selective serotonin 2C receptor agonist that can induce weight loss without valvulopathy [126]. Lorcaserin was evaluated by the FDA in 2010 but rejected due to tumor formation in rats.

Contrave (Orexigen), a combination of two well-established drugs bupropion and naltrexone in a sustained-release formulation, is also seeking approval as an antiobesity agent. The pharmacologic effect of this medication is to stimulate hypothalamic POMC neurons with bupropion while also blocking opiate-mediated POMC autoinhibition with naltrexone [127]. This agent was found to be safe and effective in a randomized placebo-controlled phase 3 clinical trial [127].

Exenatide, already approved for use in T2DM, has been demonstrated to reduce caloric intake and induce weight loss when combined with lifestyle changes [128]. The GLP-1 analog, liraglutide, currently approved for the treatment of T2DM, is being studied as a weight loss agent. In a multicenter trial of 564 nondiabetic individuals, participants lost a mean of 7.2 kg after 20 weeks of treatment with liraglutide (3.0 mg) compared with 2.8 kg with placebo and 4.1 kg with orlistat [129].

BARIATRIC SURGERY

Surgical management of class III obesity is more effective than conventional management [130]. Bariatric surgery should be considered in those adults with a BMI greater than 40 kg/m^2, where expected benefit outweighs risk, or a BMI more than 35 kg/m^2 with one or more comorbidities, where expected benefit outweighs risk. Laparoscopic bariatric procedures are safe, effective, and preferred, mainly because of shortened hospital stays and an earlier return to normal activity [131,132]. Restrictive bariatric surgical procedures, associated with reduction in obesity-related comorbidities, include the laparoscopic adjustable gastric banding (LAGB), laparoscopic RGB, and laparoscopic sleeve gastrectomy. The

LAGB procedure is associated with 44% to 68% loss of excess weight at 4 years [133,134], although 30% may fail to lose more than 30% of their excess weight [135]. The RGB procedure is associated with a 63% loss of excess weight at 1 year and 71% at 2 years [136]. One study comparing 456 patients undergoing RGB with 805 patients undergoing LAGB, performed at two different institutions, demonstrated greater excess weight loss at 18 months with RGB (74.6% vs. 40.4%) but with higher early postoperative complication rates (4.2% vs. 1.7%) [137]. The biliopancreatic diversion with duodenal switch (BPD-DS) is a combined restrictive and malabsorptive procedure associated with greater long-term loss of excess weight (61%–77% within 3 years) but at the expense of greater complication and nutritional deficiency rates [132,138,139]. In a PRCT involving 60 patients with BMI 50 to 60 kg/m^2 ("super obese") treated with BPDDS versus RGB, the perioperative safety was comparable, though greater weight loss was observed in the BPDDS group [140]. Newer nonsurgical bariatric procedures are being developed that promote weight loss prior to a bariatric surgical procedure in order to decrease postoperative complications [141]. For instance, cutaneous gastric electrical stimulation at a tachygastrial frequency increases postprandial fullness/satiety and delays gastric emptying [142]. Sleeve gastrectomy is the newest procedure. In one recent study, average excess body weight loss was 38.6% and 49.4% at 6 months and 1 year, respectively [143]. Behrens et al. [144] demonstrated resolution in 74% of patients with T2DM, 53% with hypertension, 45% with dyslipidemia, 76% with OSA, 38% with joint pain, and 20% with depression/anxiety in 34 patients with a preoperative average BMI of 50 after sleeve gastrectomy.

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This is a commentary on the Mente et al. (2010) case-controlled study and highlights the need for a definitive prospective study to clarify the question of whether clustering of risk factors (metabolic syndrome) confers an increased risk for CVD than the individual risk factors alone.

24. (4) **Lyon HN** et al. Genetics of common forms of obesity: A brief overview. Am J Clin Nutr 2005;82(suppl):215S–217S.

This is a review of the current status of genetic research and methods used to determine associations with obesity. At present, the genetics are too complex to tease out specific associations.

25. (3) **Allison DB** et al. The heritability of body mass index among an international sample of monozygotic twins reared apart. Int J Obes Relat Metab Disord 1996;20:501–506.

This is a meta-analysis of observational data from 53 pairs of monozygotic twins reared apart, demonstrating that 70% of the variance in BMI can be attributed to genetic variation.

26. (3) **Stunkard AJ** et al. The body mass index of twins who have been reared apart. N Engl J Med 1990;322:1483–1487.

This is a meta-analysis of observational data from identical and fraternal twins reared apart or together, demonstrating substantial genetic and minimal childhood environmental influences on BMI.

27. (3) **Laitinen J** et al. Family social class, maternal body mass index, childhood body mass index, and age at menarche as predictors of adult obesity. Am J Clin Nutr 2001;74: 287–294.

This is a Finnish observational study of 2,876 male and 3,404 female subjects demonstrating predictive power of low social class, high maternal BMI before pregnancy, high BMI during adolescence, and early menarche on adult obesity.

28. (4) **Prentice AM** et al. Fast foods, energy density and obesity: A possible mechanistic link. Obes Rev 2003;4:187–194.

This is a literature review of clinical studies demonstrating "passive overconsumption" of calories derived from fast foods, approximately 65% higher than in typical British diets, which challenges normal human appetite-control systems, especially in children and adolescents.

29. (4) **Drewnowski A** et al. Dietary energy density and body weight: Is there a relationship? Nutr Rev 2004;62:403–413.

In this review of the literature, insufficient longitudinal cohort or prospective epidemiologic studies demonstrated a causal association between dietary energy density and obesity risk, even though a link is supported by the findings of several cross-sectional epidemiologic studies.

30. (3) **Willett WC**. Dietary fat plays a major role in obesity: No. Obes Rev 2002;3:59–68.

In between-population and within-population cross-sectional epidemiologic studies, an association of dietary fat occurs with the prevalence of obesity. Some short-term small, randomized prospective studies even support this association, but a meta-analysis of long-term trials (>1 year) fails to demonstrate this association. Moreover, during a time period in the United States when the percentage of energy consumed derived from fat has decreased, the prevalence of obesity has substantially increased. Thus, focusing on dietary fat intake as a priority in the dietary management of obesity may be a "serious distraction."

31. (3) **Blundell JE** et al. Resistance and susceptibility to weight gain: Individual variability in response to a high-fat diet. Physiol Behav 2005;86:614–622.

In this small observational study, biologic vulnerability for obesity due to a high-fat diet is associated with symptoms that may be part of a "thrifty phenotype": weak satiety response to fatty meals, preference for high-fat foods, and a strong hedonic attraction to palatable foods and eating.

32. (3) **Song WO** et al. Is consumption of breakfast associated with body mass index in US adults? J Am Diet Assoc 2005;105:1373–1382.

In this analysis of data from the NHANES 1999–2000 involving 4,218 participants (2,097 men and 2,121 women), inclusion of a ready-to-eat cereal in the breakfast meal was associated with a decreased odds ratio (0.70) for BMI of 25 kg/m^2 or more and inverse association with BMI ($r = -0.37$; $p < 0.01$) in women, but not in men.

33. (4) **Ruxton CH** et al. Breakfast: A review of associations with measures of dietary intake, physiology and biochemistry. Br J Nutr 1997;78:199–213.

In this review of the literature, the association of breakfast and nutritional status is discussed.

34. (2) **Brondel L** et al. Acute partial sleep deprivation increases food intake in healthy men. Am J Clin Nutr 2009;91:1550–1559.

This is a prospective randomized two-condition crossover study on 12 men. Interpretation of the conclusions is limited by the small sample size, inability to generalize beyond healthy men, lack of precise energy expenditure measurements, and relatively brief sleep restriction period.

35. (2) **Cizza G** et al. Treatment of obesity with extension of sleep duration: A randomized, prospective, controlled trial. Clin Trials 2010;7:274–285.

This is a progress report on a randomized, nonblinded behavioral study.

36. (4) Dandona P et al. Metabolic syndrome. Circulation 2005;111:1448–1454.

This is a review of the competing roles of obesity and insulin resistance in the pathogenesis of metabolic syndrome.

37. (2) **de las Fuentes** et al. Effect of moderate diet-induced weight loss and weight regain on cardiovascular structure and function. J Am Coll Cardiol 2009;54:2376–2381.

In this PRCT of 60 patients receiving either a low-fat or low-carb diet, weight loss and cardiovascular benefits were dependent on overall caloric intake and not macronutrient content. A physical activity program was not part of this study.

38. (2) **Shea MK** et al. The effect of randomization to weight loss on total mortality in older overweight and obese adults: The ADAPT study. J Gerontol A Biol Sci Med Sci 2010;65A:519–525.

This is a single-blind randomized controlled interventional trial of 316 subjects. The intervention target was 5% loss of baseline weight in 18 months with dietary changes, behavioral modification, and increased physical activity.

39. (2) **Ryan DH** et al. Nonsurgical weight loss for extreme obesity in primary care settings. Arch Int Med 2010;170:146–154.

In this PRCT, 597 volunteers received either intensive medical therapy or the usual care condition. Even though the protocols were pragmatic in the treatment arm, they were still subjective on the part of the physician.

40. (2) **Balagopal P** et al. Lifestyle-only intervention attenuates the inflammatory state associated with obesity: A randomized controlled study in adolescents. J Pediatr 2005;146:342–348.

In this small PRCT of only 15 obese adolescents, increased physical activity and calorie restriction for 3 months was associated with decreased C-reactive protein, fibrinogen, and interleukin-6 levels.

41. (2) **Messier V** et al. Effects of the addition of a resistance training programme to a caloric restriction weight loss intervention on psychosocial factors in overweight and obese post-menopausal women: A Montreal Ottawa New Emerging Team study. J Sports Sci 2010;28:83–92.

One hundred thirty-seven otherwise healthy subjects were studied, but adherence to the diet and appetite was not analyzed or controlled for, thus limiting interpretation of the results.

42. (1) **Wadden TA** et al. Treatment of obesity by very low calorie diet, behavior therapy, and their combination: A five-year perspective. Int J Obes 1989;13(suppl 2):39–46.

In this randomized controlled study of 76 obese women, a significantly greater percentage of subjects in the behavior therapy alone (36%) and combined behavior therapy and very-low-calorie-diet conditions (32%) maintained their full end-of-treatment weight losses than in the very-low-calorie-diet-alone condition (5%).

43. (1) **Munsch S** et al. Evaluation of a lifestyle change programme for the treatment of obesity in general practice. Swiss Med Wkly 2003;133:148–154.

This is a prospective, randomized study of 122 patients from 14 general practices in Switzerland, consisting of 16 group sessions of 90 minutes each with integrated cognitive behavioral therapy.

44. (4) **Foster GD** et al. Behavioral treatment of obesity. Am J Clin Nutr 2005;82:230S–235S.

This is a review of clinical data on behavioral treatments for obesity.

45. (2) **Foster GD** et al. The effects of a commercially available weight loss program among obese patients with type 2 diabetes: A randomized study. Postgrad Med 2009;121:113–118.

This is a randomized trial of 69 patients, but the relatively short study period of 3 to 6 months limits interpretation of the results.

46. (3) **Ma J** et al. Evaluation of lifestyle interventions to treat elevated cardiometabolic risk in primary care (E-LITE): A randomized controlled trial. BMC Fam Pract 2009;10:71.

This is a progress report of a three-arm randomized controlled clinical trial evaluating IT-assisted self-management and care management by a dietitian and exercise counselor in overweight/obese adults with prediabetes and/or metabolic syndrome.

47. (1) **Maruthur NM** et al. Lifestyle interventions reduce coronary heart disease risk results from the PREMIER trial. Circulation 2009;119:2026–2031.

In this study, 810 healthy adults with untreated prehypertension or stage I hypertension are randomized to advice-only, established lifestyle recommendations, or established-plus-DASH diet group.

48. (2) **Kalter-Leibovici O** et al. Lifestyle intervention in obese Arab women. Arch Int Med 2010;170:970–976.

In this PRCT, social norms for male and female roles in society were addressed as well as having meetings with community and religious leaders. Local dishes were incorporated.

49. (2) **Siegel JM** et al. A worksite obesity intervention: Results from a group-randomized trial. Am J Public Health 2010;100:327–333.

This is a PRCT involving 16 school worksites and several health promotion activities.

50. (2) **Silva MN** et al. Using self-determination theory to promote physical activity and weight control: A randomized controlled trial in women. J Behav Med 2010;33: 110–122.

This is a 1-year PRCT of 239 woman incorporating autonomous forms of exercise regulation and intrinsic motivations compared with a general health educational program. Limitations of the study are the nature of the comparator group intervention, lack of a baseline comparison, and lack of an economic (cost-effectiveness) analysis for the intervention.

51. (2) **Lapointe A** et al. Using restrictive messages to limit high-fat foods or nonrestrictive messages to increase fruit and vegetable intake: What works better for postmenopausal women? Eur J Clin Nutr 2010;64:194–202.

Sixty-eight patients were randomly assigned to the two different approaches.

52. (3) **Clark EN** et al. Effects of daily snack food intake on food reinforcement depend on body mass index and energy density. Am J Clin Nutr 2010;91:300–308.

This was an observational study of 53 obese, overweight, and nonobese women.

53. (1) **Epstein LH** et al. Ten-year outcomes of behavioral family-based treatment for childhood obesity. Health Psychol 1994;13:373–383.

Based on a meta-review of four randomized studies of obese children, at 10 years, 34% had decreased their percentage overweight by more than 20%. Thirty percent of patients were not obese. The role of family and friend support for eating and activity habits is emphasized.

54. (2) **Otten JJ** et al. Effect of television viewing reduction on energy intake and expenditure in overweight and obese adults. Arch Int Med 2009;169:2109–2115.

This is a PRCT of 36 adults with BMI 25 to 50 reporting minimum of 3 hr/d of viewing. The treatment group was electronically "locked out" so that viewing was reduced by 50%.

55. (2) **Lindahl B** et al. Improved fibrinolysis by intense lifestyle intervention: A randomized trial in subjects with impaired glucose tolerance. J Intern Med 1999;246:105–112.

In this nonblinded randomized trial of 186 obese patients with impaired glucose tolerance, sustained benefits in fibrinolysis biomarkers were observed with behavioral therapy compared with usual care.

56. (2) **Esposito K** et al. Effect of weight loss and lifestyle changes on vascular inflammatory markers in obese women: A randomized trial. JAMA 2003;289:1799–1804.

In this randomized, single-blind trial of 120 premenopausal nondiabetic obese women adhering to a low-energy Mediterranean diet and increased physical activity and losing more than 10% of their weight, biomarkers for vascular inflammation and insulin resistance were reduced.

57. (2) **Wadden TA** et al. Benefits of lifestyle modification in the pharmacologic treatment of obesity: A randomized trial. Arch Intern Med 2001;161:218–227.

In this nonblinded randomized trial of 53 obese women, sibutramine alone, sibutramine plus lifestyle modification, and sibutramine, lifestyle, and portion-controlled diet induced a 4.1%, 10.8%, and 16.5% weight loss, respectively.

58. (2) **Hoeger KM** et al. A randomized, 48-week, placebo-controlled trial of intensive lifestyle modification and/or metformin therapy in overweight women with polycystic ovary syndrome: A pilot study. Fertil Steril 2004;82:421–429.

This is a PRCT limited by recruitment, dropout, and compliance. Patients treated with both lifestyle changes and metformin lost more weight than those with either intervention alone.

59. (2) **Schroder KE**. Computer-assisted dieting: Effects of a randomized controlled intervention. Psychol Health 2010;25:519–534.

In this PRCT, there were three groups: initial computer-assisted dieting (CAD) session with software provided, CAD and a self-management program, and controls. Follow-up was limited to just 6 months.

60. (2) **Temple JL** et al. Nutrition labels decrease energy intake in adults consuming lunch in the laboratory. J Am Diet Assoc 2010;110(7):1094–1097.

In this small (N = 47) prospective study randomizing subjects to video educational materials and labeling conditions, less energy intake was consumed from both low- and high-energy-containing foods in the nutrition-labeling group. Interpretation of these findings is limited by the small number of subjects who were obese and the specific foods available for selection.

61. (2) **Guelinckx I** et al. Effect of lifestyle intervention on dietary habits, physical activity, and gestational weight gain in obese pregnant women: A randomized controlled trial. Am J Clin Nutr 2010;91:373–380.

This is a PRCT of 195 pregnant women, in which participants in the control arm knew they were in a health promotion study. This may have influenced their records. Also, the dropout rate was relatively high, and the nutritional data were incomplete.

62. (2) **Spring B** et al. Randomized controlled trial for behavioral smoking and weight control treatment: Effect of concurrent versus sequential intervention. J Consult Clin Psychol 2004;72:785–796.

This randomized trial of 315 female smokers found that weight control added to the last, versus the first, 8 weeks of a 16-week smoking cessation was associated with a more lasting and stable weight suppression effect. The study is limited by inclusion of only highly motivated female subjects.

63. (2) **Mavri A** et al. Effect of diet-induced weight loss on endothelial dysfunction: Early improvement after the first week of dieting. Heart Vessels 2011;26(1):31–38.

This study of matched obese (40) and control subjects (20) receiving low-calorie diet for 5 months found favorable effects on markers of endothelial function. The study is limited by a high dropout rate.

64. (1) **Johansson K** et al. Effect of a very low energy diet on moderate and severe obstructive sleep apnoea in obese men: A randomized controlled trial. BMJ 2009;339:b4609.

This is a prospective randomized controlled study of 63 obese men with moderate to severe OSA.

65. (4) **Institute of Medicine**. Dietary, functional, and total fiber: Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids. Washington, DC: National Academy Press, 2002:265–334.

This is an official evidence-based resource with tables for easy referencing. The website can be navigated to access information about all aspects of dietary guidelines: http://www.iom.edu/report.asp?id=4340 (Accessed on October 30, 2005).

66. (2) **Strik CM** et al. No evidence of differential effects of SFA, MUFA or PUFA on post-ingestive satiety and energy intake: a randomized trial of fatty acid saturation. Nutr J 2010;9:24.

In this three-treatment randomized crossover design, there was no difference among the groups in consumption of the next meal 3.5 hours later. The study population was 18 lean healthy men, limiting interpretation of the results when considering patients with obesity.

67. (4) **Ello-Martin JA** et al. The influence of food portion size and energy density on energy intake: Implications for weight management. Am J Clin Nutr 2005;82(1 suppl): 236S–241S.

Review of controlled prospective clinical studies concluding that low-energy-dense foods intake suppresses appetite and limits calorie consumption for up to 2 days.

68. (2) **Maki KC** et al. Whole-grain ready-to-eat cereal, as part of a dietary program for weight loss, reduces low-density lipoprotein cholesterol in adults with overweight and obesity more than a dietary program including low-fiber control foods. J Am Diet Assoc 2010;110:205–214.

In this randomized, parallel-arm controlled trial, 204 overweight/obese patients received 3 g/d of oat β-glucan or energy-matched low-fiber control food as part of a −500 kcal/d, low energy and saturated fat, increased physical activity program. The amount of weight loss was small, and it is possible that other factors (physical activity and low-energy diet) contributed to the main effects, in addition to role of fiber.

69. (3) **DellaValle DM** et al. Does the consumption of caloric and non-caloric beverages with a meal affect energy intake? Appetite 2005;44:187–193.

In this study, 44 women were observed eating lunch over a 6-week course in which different beverages were provided. When caloric beverages were consumed with lunch, the total energy

intake was on average 104 ± 16 kcal greater, without any effect on satiety, than when noncaloric beverages were consumed.

70. (1) **Foster GD** et al. A randomized trial of a low-carbohydrate diet for obesity. N Engl J Med 2003;348:2082–2090.

    This 1-year randomized multicenter controlled trial of 63 obese men and women demonstrated greater weight loss at 3 and 6 months (about 4% difference in weight), but not by 1 year, of a low-carbohydrate, high-protein, high-fat diet compared with a conventional low-calorie, high-carbohydrate, low-fat diet.

71. (1) **Yancy WS** et al. A low-carbohydrate, ketogenic diet versus a low-fat diet to treat obesity and hyperlipidemia. Ann Intern Med 2004;140:769–777.

    This is a randomized controlled trial of 120 overweight hyperlipidemic subjects over 24 weeks demonstrating greater weight loss (−12.9% vs. −6.7%) and adherence (76% vs. 57%) of a low-carbohydrate diet (<20 g carbohydrate initially) compared with a low-fat diet (<30% fat calories, <300 mg daily cholesterol, 500 to 1,000 kcal/d energy deficit). Greater improvements in hypertriglyceridemia and low HDL levels were also observed in the low-carbohydrate group.

72. (1) **Brehm BJ** et al. A randomized trial comparing a very low carbohydrate diet and a calorie-restricted low fat diet on body weight and cardiovascular risk factors in healthy women. J Clin Endocrinol Metab 2003;88:1617–1623.

    In this randomized controlled trial of 53 healthy obese subjects over a 6-month period, greater weight loss (8.5 vs. 3.9 kg) and fat-mass loss (4.8 vs. 2.0 kg) was observed with an ad libitum low-carbohydrate diet versus a calorie-restricted diet with 30% of calories as fat. No differences were found between the groups of calories consumed, lipids, fasting glucose, insulin, or blood pressure, although the low-carbohydrate group had higher β-hydroxybutyrate levels.

73. (1) **Samaha FF** et al. A low-carbohydrate as compared with a low-fat diet in severe obesity. N Engl J Med 2003;348:2074–2081.

    In this randomized controlled trial of 79 obese subjects (39% with diabetes and 43% with metabolic syndrome) over a 6-month period, greater weight loss (−5.8 vs. −1.9 kg) was observed with a low-carbohydrate diet compared with a calorie-restricted low-fat diet. Improvements in hypertriglyceridemia and insulin resistance were greater in the low-carbohydrate group.

74. (1) **Stern L** et al. The effects of low-carbohydrate versus conventional weight loss diets in severely obese adults: One-year follow-up of a randomized trial. Ann Intern Med 2004;140:778–785.

    This study reports the 1-year follow-up data from the study by Samaha FF, et al. (2003). Weight loss differences at 6 months were not present at 1 year, although lipid and glycemic status (A_{1c} levels) remained better in the low-carbohydrate group.

75. (1) **Barnard ND** et al. The effects of a low-fat, plant-based dietary intervention on body weight, metabolism, and insulin sensitivity. Am J Med 2005;118:991–997.

    In this randomized controlled study of 64 overweight postmenopausal women over a 14-week period, an ad libitum low-fat vegan diet was associated with greater weight loss (5.8 vs. 3.8 kg) compared with an NCEP control diet.

76. (1) **Pirozzo S** et al. Advice on low-fat diets for obesity (Cochrane Review): The Cochrane Library, 2005; Issue 2. http://www.cochrane.org/cochrane/revabstr/AB003640.htm (accessed 11/8/2005).

    In this meta-analysis of four PRCTs with 6-month follow-up, five with 12-month follow-up, and three with 18-month follow-up, no significant differences in weight loss or other clinical parameters were noted between those overweight/obese patients treated with a low-fat diet compared with other weight-reducing calorically restricted diets.

77. (2) **Grau K** et al. *TCF7L2* rs7093146-macronutrient interaction in obese individuals' responses to a 10-wk randomized hypoenergetic diet. Am J Clin Nutr 2010;91:472–479.

    This is a PRCT involving 771 European obese patients. The post hoc analyses and modeling as well as beta error due to sample size limit interpretation of the findings. This is one of many candidate loci being studied in patients with obesity or T2DM.

78. (2) **Nickols-Richardson SM** et al. Perceived hunger is lower and weight loss is greater in overweight premenopausal women consuming a low-carbohydrate/high-protein vs high-carbohydrate/low-fat diet. J Am Diet Assoc 2005;105:1433–1437.

    In this small 6-week PRCT involving 28 overweight premenopausal women, a low-carbohydrate/high-protein diet was associated with decreased hunger perception and greater percentage of body weight loss.

79. (4) **Schoeller DA** et al. Energetics of obesity and weight control: Does diet composition matter? J Am Diet Assoc 2005;105(suppl 1):S24–S28.

    This is a review of the clinical literature and a commentary drawing the following conclusions: (1) that prior studies demonstrating an advantage of low-carbohydrate diets by virtue of

decreased calorie intake are flawed and studies involving 24-hour energy expenditures are not supportive of this claim; (2) that it is speculated that it is the high-protein content of a therapeutic diet that suppresses appetite and leads to weight loss, rather than a low-carbohydrate component; and (3) that hypocaloric weight loss diets should contain 35% to 50% carbohydrate, 25% to 35% fat, and 25% to 30% protein, based on total daily energy needs.

80. (1) **Moran LJ** et al. The satiating effect of dietary protein is unrelated to postprandial ghrelin secretion. J Clin Endocrinol Metab 2005;90:5205–5211.

    In this 12-week randomized, parallel-design controlled study of 57 overweight, hyperinsulinemic men and women, comparable effects of high-protein (34%)/low-fat (29%) and standard protein (18%)/high-fat (45%) diets were seen: Both were associated with decreased appetite, increased ghrelin, and decreased weight.

81. (1) **Noakes M** et al. Effect of an energy-restricted, high-protein, low-fat diet relative to a conventional high-carbohydrate, low-fat diet on weight loss, body composition, nutritional status, and markers of cardiovascular health in obese women. Am J Clin Nutr 2005;81:1298–1306.

    In this randomized controlled study of 100 obese or overweight women over a 12-week period, an energy-restricted high-protein, low-fat diet was associated with greater fat-mass loss and improvements in glycemic and lipid status compared with a high-carbohydrate diet, despite no differences in weight loss.

82. (2) **Pal S** et al. Effects of whey protein isolate on body composition, lipids, insulin and glucose in overweight and obese individuals. Br J Nutr 2010;104:716–723.

    In this randomized, parallel design trial, 89 patients, blinded to treatment, received the same dosing of whey protein, sodium caseinate, or a glucose control. One limitation of the study was the self-reporting of energy intake by patients.

83. (3) **Reddy ST** et al. Effect of low-carbohydrate high-protein diets on acid-base balance, stone-forming propensity, and calcium metabolism. Am J Kidney Dis 2002;40: 265–274.

    In 10 healthy subjects, adherence to the Atkins' induction diet for 2 weeks (1,930 mean kcal/d, 164 mean g protein/d, 133 mean g fat/d, and 19 mean g carbohydrate/d) followed by the Atkins' maintenance diet (2,034 mean kcal/d, 170 mean g protein/d, 136 mean g fat/d, and 33 mean g carbohydrate/d) was associated with increased urinary acid and calcium excretion, decreased urinary citrate levels, and a trend toward increased bone resorption and decreased bone formation.

84. (4) **Amanzadeh J** et al. Effect of high protein diet on stone-forming propensity and bone loss in rats. Kidney Int 2003;64:2142–2149.

    This is a rat study demonstrating the hypocitraturic and bone hyperresorptive effects of a high-protein 60 diet.

85. (2) **Bowen J** et al. A high dairy protein, high-calcium diet minimizes bone turnover in overweight adults during weight loss. J Nutr 2004;134:568–573.

    In this nonblinded randomized study, 50 subjects received 12 weeks of a high-protein, energy-restricted diet, with either 2,400 mg/d calcium (using dairy protein sources) or 500 mg/d calcium (using mixed protein sources), followed by a 4-week period of energy balance. Weight loss (10% initial body weight) was comparable between the two groups, but the dairy protein group had less bone hyperresorption than the mixed-protein group.

86. (4) **Friedman AN** et al. High-protein diets: Potential effects on the kidney in renal health and disease. Am J Kidney Dis 2004;44:950–962.

    In this review of the clinical literature represented by human interventional studies, all but one being randomized, high-protein diets were found to pose significant harm in patients with chronic kidney disease: increased proteinuria, diuresis, natriuresis, kaliuresis, blood pressure changes, and nephrolithiasis.

87. (2) **Brinkworth GD** et al. Renal function following long-term weight loss in individuals with abdominal obesity on a very-low carbohydrate diet vs high carbohydrate diet. J Am Diet Assoc 2010;110:633–638.

    In this PRCT, weight loss was similar between the treatment and control groups. The interpretation of results is limited by the relatively small sample size, follow-up for only a year (since aging and weight loss also affect renal function, many have argued follow-up >3 years is needed), and the use of predictive equations to estimate the GFR.

88. (1) **Dansinger ML** et al. Comparison of the Atkins, Ornish, Weight Watchers, and Zone Diets for weight loss and heart disease risk reduction. JAMA 2005;293:43–53.

    Blinded randomized study of 160 patients finding that it is adherence to a diet that has the greater effect on success. The caloric reduction among the four groups, which had comparable weight loss overall, were 138 kcal/d (Atkins), 251 kcal/d (Zone), 244 kcal/d (Weight Watchers), and 192 kcal/d (Ornish) ($p < 0.05$).

89. (2) **Foster GD** et al. Weight and metabolic outcomes after 2 years on a low-carbohydrate versus low-fat diet. Ann Intern Med 2010;153;147–157.

This multicenter randomized controlled parallel group trial extended follow-up similarly designed studies to 2 years but was limited by a large dropout rate. Patients with diabetes and dyslipidemia were excluded from the study.

90. (2) **Wycherley TP** et al. Long-term effects of weight loss with a very low carbohydrate and low fat diet on vascular function in overweight and obese patients. J Intern Med 2010;267:452–461.

This is a relatively small PRCT of 49 overweight/obese patients receiving an energy-reduced low-carbohydrate or low-fat diet for only 1 year. Weight losses were similar between the two groups. It is unclear from this study endpoints whether the rate of cardiovascular events is affected by either intervention.

91. (2) **Bradley U** et al. Effects on weight loss, insulin resistance, and cardiovascular risk: A randomized control trial. Diabetes 2009;58:2741–2748.

This 8-week randomized controlled trial of 24 overweight/obese subjects compared low-fat (20%) with low-carbohydrate (20%) hypocaloric (500 kcal/d deficit) diets.

92. (3) **Zahouani A** et al. Short- and long-term evolution of body composition in 1,389 obese outpatients following a very low calorie diet (Pro'gram18 VLCD). Acta Diabetol 2003;40(suppl 1):S149–S150.

In this large observational study, a VLCD was associated with weight loss maintenance and improved obesity-associated risk factors for up to 2 years.

93. (2) **Davis LM** et al. Efficacy of meal replacement diet plan compared to a food-based diet plan after a period of weight loss and weight maintenance: A randomized controlled trial. Nutritional J 2010;9:11.

This is an unblinded 40-week PRCT of 80 obese patients (16 week program + 24 week weight maintenance). There was a typically high dropout rate of 43%, comparable with other studies.

94. (1) **Heymsfield SB** et al. Weight management using a meal replacement strategy: Meta- and pooling analysis from six studies. Int J Obes Relat Metab Disord 2003;27:537–549.

These meta-analyses of PRCTs for more than 3 months of adult subjects with BMI of 25 kg/m^2 or more demonstrate safety and efficacy of partial meal replacements on weight loss and reduction of obesity-associated risk factors.

95. (3) **Arunabh S** et al. Body fat content and 25-hydroxyvitamin D levels in healthy women. J Clin Endocrinol Metab 2003;88:157–161.

In this cross-sectional study of 410 healthy women with BMIs ranging from 17 to 30 kg/m^2, an inverse correlation was found between percentage body fat (determined by DEXA) and 25-hydroxyvitamin D levels. This relation is thought to be due to an increased tissue distribution of vitamin D with increased adiposity.

96. (3) **Buffington C** et al. Vitamin D deficiency in the morbidly obese. Obes Surg 1993;3: 421–424.

In this cross-sectional study of 60 obese women being considered for bariatric surgery, 25-hydroxyvitamin D levels were negatively correlated with obesity.

97. (4) **Dwyer JT** et al. Dietary supplements in weight reduction. J Am Diet Assoc 2005;105:S80–S86.

A review of weak clinical trials involving dietary supplements and obesity demonstrates inconclusive evidence for any benefit.

98. (2) **Basu A** et al. Blueberries decrease cardiovascular risk factors in obese men and women with metabolic syndrome. J Nutr 2010;140:1582–1587.

In this 8-week PRCT of 48 patients with metabolic syndrome, consumption of a freeze-dried blueberry beverage was associated with significant reductions in systolic and diastolic BP, oxidized LDL cholesterol, and markers of lipid peroxidations but without changes in glucose levels. This study was composed primarily of women and had a relatively high dropout rate, primarily due to the high fiber content in the treatment arm. Also, it is not clear whether the benefits were due to the fiber or polyphenol content (or both) of the treatment beverage.

99. (2) **Shenoy SF** et al. Weight loss in individuals with metabolic syndrome given DASH diet counseling when provided a low sodium vegetable juice: A randomized controlled trial. Nutr J 2010;9:8.

Patients had metabolic syndrome and were randomized to consuming 0, 8, or 16 fluid ounces a day of juice with a calorie-restricted DASH diet (1,600 kcal/d for women and 1,800 kcal/d for men).

100. (3) **Papanikolaou Y** et al. Bean consumption is associated with greater nutrient intake, reduced systolic blood pressure, lower body weight, and a smaller waist circum-

ference in adults: Results from the National Health and Nutrition Examination Survey 1999–2002. J Am Coll Nutr 2008;27:569–576.

This is an epidemiologic study.

101. (3) **Sichieri R**. Dietary patterns and their associations with obesity in the Brazilian city of Rio de Janeiro. Obesity Res 2002;10:42–48.

This is an epidemiologic study.

102. (2) **Wong CL** et al. Food intake and satiety following a serving of pulses in young men: effect of processing, recipe, and pulse variety. J Am Coll Nutr 2009;28:543–552.

In this randomized, repeated measures designed, short-term effects on appetite and food intake were not affected by consumption of navy bean–containing dishes.

103. (4) Department of Health and Human Services and the U.S. Department of Agriculture. Dietary guidelines for Americans, 2005. http://www.health.gov/dietaryguidelines/dga2005/document/pdf/dga2005.pdf. Accessed on October 30, 2005.

This is the complete evidence-based review, with specific recommendations on healthy eating and lifestyle, including physical activity.

104. (1) **Ross R** et al. Reduction in obesity and related comorbid conditions after diet-induced weight loss or exercise-induced weight loss in men: A randomized, controlled trial. Ann Intern Med 2000;133:92–103.

In this randomized controlled trial of 52 obese men over a 3-month period, daily physical activity without calorie restriction reduced abdominal obesity and insulin resistance.

105. (2) **Yassine HN** et al. Effects of exercise and caloric restriction on insulin resistance and cardiometabolic risk factors in older obese adults—a randomized clinical trial. J Gerontol A Biol Sci Med Sci 2009;64A: 90–95.

This is a prospective randomized controlled trial on 24 older obese adults with metabolic syndrome.

106. (2) **Christiansen T** et al. Exercise training versus diet-induced weight-loss on metabolic risk factors and inflammatory markers in obese subject: A 12-week randomized intervention study. Am J Physiol Endocrinol Metab 2010;298:E824–E831.

This unblinded PRCT of 69 subjects still raises the possibility that more intense physical activity/exercise may have significant and relevant effects on obesity-related inflammation.

107. (2) **Ibanez J** et al. Resistance training improves cardiovascular risk factors in obese women despite a significant decrease in serum adiponectin levels. Obesity 2010;18:535–541.

This is an unblinded RCT of 34 obese women receiving a weight loss diet (−500 kcal/d) with or without a 16-week progressive resistance training program twice a week versus a control group. The findings and interpretations were confounded by the differing menstrual cycle status of the subjects.

108. (1) **Slentz** et al. Effects of the amount of exercise on body weight, body composition, and measures of central obesity: STRRIDE: A randomized controlled study. Arch Intern Med 2004;164:31–39.

In this randomized controlled trial of 120 subjects over an 8-month period, a dose-dependent effect of physical activity on weight loss was found, independent of diet.

109. (1) **Lindstrom J** et al. The Finnish Diabetes Prevention Study (DPS): Lifestyle intervention and 3-year results on diet and physical activity. Diabetes Care 2003;26:3230–3236.

This is a randomized controlled trial over a 3-year period of 522 middle-aged overweight subjects with impaired glucose tolerance, demonstrating that intensive lifestyle intervention for the first year followed by a maintenance period (diet and exercise) produces greater weight loss and reduced diabetes risk compared with usual care.

110. (1) **Jeffery RW** et al. Physical activity and weight loss: Does prescribing higher physical activity goals improve outcome? Am J Clin Nutr 2003;78:684–689.

This is a randomized controlled trial of 202 overweight men and women found to have greater long-term (18 months) weight loss with more exercise (2,500 kcal/wk) compared with less exercise (1,000 kcal/wk).

111. (1) **Jakicic JM** et al. Effect of exercise duration and intensity on weight loss in overweight, sedentary women: A randomized trial. JAMA 2003;290:1323–1330.

In this randomized controlled trial of 201 sedentary women followed up for 12 months, a dose–response effect of exercise with weight loss was noted.

112. (2) **Molenaar EA** et al. Effect of nutritional counseling and nutritional plus exercise counseling in overweight adults: A randomized trial in multidisciplinary primary care practice. Fam Pract 2010;27(2):143–150.

This is a PRCT of 134 overweight/obese adults randomized to nutritional ± nutritional/exercise counseling and followed for 12 months. A full factorial design was not implemented

in the design of this study (nutritional counseling included some advice regarding physical activity), limiting interpretation of the findings.

113. (2) **Wycherley TP** et al. A high-protein diet with resistance exercise training improves weight loss and body composition in overweight and obese patients with type 2 diabetes. Diabetes Care 2010;33:969–976.

    This study compared four groups (isocaloric diets with or without high protein and with or without resistance exercise). There were increased dropouts in the high-protein group for unclear reasons. These findings are applicable to overweight/obese patients with type-2 diabetes.

114. (3) **Erdmann J** et al. Effect of carbohydrate- and protein-rich meals on exercise-induced activation of lipolysis in obese subjects. Horm Metab Res 2010;42:290–294.

    This is a prospective cohort trial with a small sample size.

115. (3) **Li Z** et al. Meta-analysis: Pharmacologic treatment of obesity. Ann Intern Med 2005;142:532–546.

    The authors performed meta-analyses based on information from electronic databases, experts in the field, and unpublished reports on sibutramine, phentermine, diethylpropion, orlistat, fluoxetine, bupropion, topiramate, sertraline, and zonisamide.

116. (1) **Padwal R** et al. Long-term pharmacotherapy for obesity and overweight. The Cochrane Database Syst Rev 2005; Issue 3. http://www.cochrane.org/reviews/en/ab004094.html (accessed on 11/8/2005).

    This is a meta-analysis demonstrating weight loss with orlistat (11 PRCTs >1 year; 2.7-kg loss, 2.9% more weight loss than controls; 12% patients with >10% weight loss) and sibutramine (five PRCTs >1 year; 4.3-kg loss, 4.6% more weight loss than controls; 15% patients with >10% weight loss). Attrition rates were high: 33% for orlistat and 43% for sibutramine.

117. (1) **Cavaliere H** et al. Gastrointestinal side effects of orlistat may be prevented by concomitant prescription of natural fibers (psyllium mucilloid). Int J Obes Relat Metab Disord 2001;25:1095–1099.

    This is a randomized, placebo-controlled study of 60 obese women in which 6 g of psyllium mucilloid decreased gastrointestinal symptoms associated with orlistat (120 mg PO t.i.d.) use.

118. (1) **James WPT** et al. Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. New Engl J Med 2010;363:905–917.

    This is a well-designed prospective, double-blind, randomized trial of 9,804 subjects at relatively high risk for CVD events.

119. (1) **Wilding J** et al. A randomized double-blind placebo-controlled study of the long-term efficacy and safety of topiramate in the treatment of obese subjects. Int J Obes Relat Metab Disord 2004;28:1399–1410.

    This is a randomized controlled trial of 1,289 overweight or obese subjects with 6-week run-in, 8-week titration, and 2-year maintenance phases. After 1 year, improvements were seen in weight loss, blood pressure, and glycemic control.

120. (1) **Astrup A** et al. Topiramate: Long-term maintenance of weight loss induced by a low-calorie diet in obese subjects. Obes Res 2004;12:1658–1669.

    This is a randomized controlled trial of 701 obese subjects who had already lost weight on a low-calorie diet for 8 weeks and continued with lifestyle changes and topiramate or placebo. Topiramate was associated with increased weight loss and was well tolerated.

121. (1) **Bray GA** et al. A 6-month randomized, placebo-controlled, dose-ranging trial of topiramate for weight loss in obesity. Obes Res 2003;11:722–733.

    This is a randomized controlled trial of 385 healthy obese patients found to have greater weight loss with topiramate, compared with placebo, at 64-, 96-, 192-, and 384-mg daily doses.

122. (1) **McElroy SL** et al. Topiramate in the treatment of binge eating disorder associated with obesity: A randomized, placebo-controlled trial. Am J Psychiatry 203;160:255–261.

    This randomized controlled study of 61 obese patients with binge-eating disorder over a 14-week period demonstrated decreased weight and binge frequency compared with placebo.

123. (3) **Guerdjikova AI** et al. Response of recurrent binge eating and weight gain to topiramate in patients with binge eating disorder after bariatric surgery. Obes Surg 2005;15:273–277.

    This is a report of three patients treated successfully with topiramate for an average of 10 months.

124. **Wellmer J** et al. The impact of zonisamide on weight. A clinical study in 103 patients with epilepsy. Acta Neurol Scand. 2009;119(4):233–238.

125. **Gadde KM** et al. Zonisamide for weight loss in obese adults: A randomized controlled trial. JAMA 2003;289:1820–1825.

126. (1) **Smith SR** et al. Multicenter, placebo-controlled trial of lorcaserin for weight management. New Engl J Med 2010;363:245–256.

This is a randomized, double-blind controlled trial of 3,182 overweight/obese subjects using lorcaserin 10 mg PO b.i.d. and behavioral modification for 1 to 2 years. Primary endpoints were weight loss at 1 year and weight maintenance at 2 years.

127. (1) **Greenway FL** et al. Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): A multicentre, randomized, double-blind, placebo-controlled, phase 3 trial. Lancet 2010;376:595–605.

One thousand seven hundred forty-two subjects were enrolled. The major adverse effect was nausea.

128. (2) **Rosenstock J** et al. Effects of exenatide and lifestyle modification on body weight and glucose tolerance in obese subjects with and without prediabetes. Diabetes Care 2010;33:1173–1175.

This is a randomized placebo-controlled study of obese patients without diabetes (N = 152) receiving a 4-week run-in period on 5 μg b.i.d. and then 4-week study period on 10 μg b.i.d. Primary analysis was based on an intent-to-treat sample. Glucose regulation also improved in patients receiving treatment.

129. **Astrup A** et al. Effects of liraglutide in the treatment of obesity: A randomized, double-blind, placebo-controlled study. Lancet 2009;374:1606–1616.

130. (1) **Colquitt J** et al. Surgery for morbid obesity: The Cochrane Database Syst Rev 2005; Issue 3. http://www.cochrane.org/reviews/en/ab003641.html (accessed 11/8/2005).

This meta-review of 18 trials, of variable quality, involving 1,891 subjects, led the authors to conclude that only limited evidence existed but that surgical management of class III obesity was more effective than nonsurgical methods.

131. (1) **Nguyen NT** et al. Laparoscopic versus open gastric bypass: A randomized study of outcomes, quality of life, and costs. Ann Surg 2001;234:279–289.

This randomized controlled study comparing open versus laparoscopic RGB in 155 patients with BMIs of 40 to 60 kg/m^2 found longer operative time, less blood loss, shorter hospital stay, more anastomotic strictures, and fewer wound-related complications with the laparoscopic approach. Weight loss was similar between the two groups.

132. (4) **Jones DB** et al. Optimal management of the morbidly obese patient. Surg Endosc 2004;18:1029–1037.

In this evidence-based report, 1,500 clinical trials were rated, and conclusions were drawn regarding the relative merits of various bariatric surgery procedures. Strong recommendations are made based on EL1 data.

133. (2) **O'Brien PE** et al. Prospective study of a laparoscopically placed, adjustable gastric band in the treatment of morbid obesity. Br J Surg 1999;86:113–118.

Prospective, single-arm study of 302 patients receiving a LAP-BAND with 4-year follow-up. Early complications occurred in 4%, mean length of stay was 3.9 days, and late complications (prolapse of stomach through band) occurred in 9%. Mean loss of excess weight was 51% at 12 months, 58.3% at 24 months, 61.6% at 36 months, and 68.2% at 48 months.

134. (3) **DeMaria EJ** et al. High failure rate after laparoscopic adjustable silicone gastric banding for treatment of morbid obesity. Ann Surg 2001;233:809–818.

This is an observational study of 36 patients receiving LAP-BAND and followed up for more than 4 years. Only four achieved a BMI less than 35 kg/m^2 or more than 50% loss of excess weight. More than 50% required band removal or conversion to RGB.

135. (3) **Favretti F** et al. Laparoscopic banding: Selection and technique in 830 patients. Obes Surg 2002;12:385–390.

In this observational study of 830 patients receiving a LAP-BAND, mortality was 0, conversion 2.7%, major complications requiring reoperation 3.9%, minor complications requiring reoperation 11%, and failure to lose more than 30% of excess weight occurred in 20%.

136. (1) **Lee WJ** et al. Laparoscopic vertical banded gastroplasty and laparoscopic gastric bypass: A comparison. Obes Surg 2004;14:626–634.

In this randomized controlled study, 80 patients with class III obesity were found to have greater loss of excess weight with RGB compared with the purely restricted vertical banded gastroplasty procedure.

137. (3) **Biertho L** et al. Laparoscopic gastric bypass versus laparoscopic adjustable gastric banding: A comparative study of 1,200 cases. J Am Coll Surg 2003;197:536–544.

This is a comparison of two case series.

138. (3) **Parikh MS** et al. Laparoscopic bariatric surgery in super-obese patients (BMI >50) is safe and effective: A review of 332 patients. Obes Surg 2005;15:858–863.

This retrospective study of super obese patients compares the three types of laparoscopic bariatric surgeries: LAP-BAND (n = 192) was associated with 35% loss of excess weight at 1 year, 46% at 2 years, and 50% at 3 years, with a 0.5% conversion rate, 60-minute operative time, 24-hour median length of stay, 4.7% morbidity, and no mortality; RGB (n = 97) was associated with 58% loss of excess weight at 1 year, 55% at 2 years, and 57% at 3 years, with a 2.1% conversion rate, 130-minute operative time, 72-hour median length of stay, 11.3% morbidity, and no mortality; BPD (with and without duodenal switch; n = 43) was associated with 61% loss of excess weight at 1 year, 69% at 2 years, and 77% at 3 years, with a 7.0% conversion rate, 255-minute operative time, 96-hour median length of stay, 16.3% morbidity rate, and no mortality.

139. (4) **Bloomberg RD** et al. Nutritional deficiencies following bariatric surgery: What have we learned? Obes Surg 2005;15:145–154.

In this review of the literature, details of nutritional deficiencies with the common bariatric procedures are provided. Malabsorptive procedures, particularly BPD > RGB, are associated with several deficiencies, with hypoproteinemia being the most significant.

140. (2) **Sovik TT** et al. Randomized clinical trial of laparoscopic gastric bypass versus laparoscopic duodenal switch for superobesity. Br J Surg 2010;97:160–166.

In this two-center PRCT, 60 patients with a BMI of 50 to 60 kg/m^2 received either BPDDS or RGB surgery. Perioperative morbidity and mortality rates were the same. BPDDS patients had greater weight loss after 1 year. The results are limited by the relatively small sample size (type II error) and follow-up for only 1 year.

141. (2) **Gersin KS** et al. Open label, sham-controlled trial of an endoscopic duodenojejunal bypass liner for preoperative weight loss in bariatric surgery candidates. Gastrointest Endosc 2010;71:976–982.

In this multicenter, prospective randomized sham-controlled trial of 47 obese patients, the duodenojejunal bypass liner was associated with statistically significant weight loss. The results are limited by the relatively small sample size, short follow-up (12-weeks), some technical challenges including a learning curve with the procedure, and lack of control for variables (e.g., dietary habits) between the two groups.

142. (2) **Wang J** et al. Effects of cutaneous gastric electrical stimulation on gastric emptying and postprandial satiety and fullness in lean and obese subjects. J Clin Gastroenterol 2010;44:335–339.

In a series of randomized trials, 20 patients were exposed to stimulation or no stimulation at physiologic or tachygastrial frequencies.

143. **Fuks D** et al. Results of laparoscopic sleeve gastrectomy: A prospective study in 135 patients with morbid obesity. Surgery. 2009;145(1):106–113.

144. **Behrens C** et al. Early results of a Canadian laparoscopic sleeve gastrectomy experience. Can J Surg. 2011;54(2):138–143.

9

Multiple Endocrine Neoplasia

Glen Sizemore and Norma Lopez

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Two sets of multiple endocrine neoplasia (MEN) syndromes and multiple tumor associations are characterized by the work of Steiner et al. [1]. Table 9.1 lists the syndrome components and their penetrance. MEN1 describes a combination of two or more tumors of pituitary, enteropancreatic, and parathyroid origin. Wermer [2] confirmed genetic origin by reporting disease in successive generations of one family. MEN2, originally described by Sipple [3], refers to the combination of medullary thyroid carcinoma (MTC), pheochromocytoma (P), and parathyroid tumors. MEN2 has three variants: MEN2A patients have a normal phenotype; MEN2B patients have a distinct phenotype (vide infra) with oral ganglioneuromas, marfanoid habitus, prominent corneal nerves, and general lack of parathyroid disease; and familial MTC (FMTC) was initially used to describe families with MTC only; currently, it is considered to be a phenotypic variant of MEN2A with decreased penetrance of P and parathyroid hyperplasia rather than a distinct entity [4].

The MEN syndromes are rare. Probably underestimated prevalence ranges from 0.2 to 2.0/100,000 for MEN1 and 2.0 to 10/100,000 for MEN2. Initially, cases were thought to be more common in people of northern European ancestry; with time, more cases are being reported from southern and eastern Europe, Asia, and, less commonly, Africa and South America. Because the patients with these diseases are limited and spread among multiple institutions, there have been no randomized double-blind studies of means to confirm diagnosis, results of different therapies, or cost-effectiveness.

Both MEN syndromes are inherited with an autosomal dominant pattern of transmission. MEN1 derives from mutations of a gene at chromosome 11q13. This gene encodes a 613-amino-acid intranuclear protein called menin, which is considered a putative tumor suppressor. In 10% of MEN1 patients, the mutation arises *de novo*, and in familial index cases of MEN1 there is a 60% to 80% prevalence of an identifiable mutation—one of approximately 800 germline codon mutations that are "inactivating" and remove tumor suppression [5,6]. If loss of the second suppressor allele occurs, tumor development begins in a manner consistent with Knudson and Strong's "two-hit" mutational model [7]. There is no genotype–phenotype correlation in MEN1.

In MEN2 patients, there may be at least 12 germline, missense, codon mutations of the RET (rearranged during transfection) protooncogene at chromosome

Table 9.1. MEN: Organ or Feature Involvement with Estimated Penetrance in Adults

Organ Involved	Estimated Penetrance
MEN1	
Parathyroid	90%
Enteropancreatic	30%–75%
Functioning	
Gastrin*	40%–50%
Insulin*	10%–29%
Glucagon	1%
Nonfunctioning	
Pancreatic polypeptide	17%–20%
Glucagon	2%–8%
Vasoactive intestinal polypeptide	2%
Somatostatin	2%
Foregut carcinoid (nonfunctional)	16%
Thymic*	2%–8%
Bronchial*	2%–8%
Gastric enterochromaffin-like	23%
Anterior pituitary	18%–47%
Prolactin	20%–30%, 60%
Growth hormone and prolactin	5%
Growth hormone	5%
Adrenocorticotropic	2%
Thyrotropin	1%
Gonadotrophins	<1%
Nonfunctional	5%–10%
Thyroid	12%
Adrenal cortex	16%–40%
Nonendocrine tumors	
Lipoma	30%
Facial angiofibroma	88%
Collagenoma	72%
Leiomyoma	10%
MEN2	
MEN2A	43%
MTC*	100%
Pheochromocytoma*	19%–50%
Parathyroid*	15%–30%
Cutaneous lichen amyloidosis	Rare
Hirschsprung disease	Rare
MEN2B	17%
MTC*	100%
Pheochromocytoma*	25%
Parathyroid*	Rare
Ganglioneuroma phenotype	100%
FAMILIAL MEDULLARY CARCINOMA	7.0%

*Tumor with malignant potential.

10q11.2. More than 95% of MEN2 cases have been found to have such mutations. This "activating" gene encodes receptor tyrosine kinases, which signal cell growth and differentiation, and it starts tumor genesis. First, a germinal mutation occurs that increases cell susceptibility to malignant transformation; the second event is a somatic mutation that transforms the mutant cell into a tumor cell. In MEN2, there is a strong genotype–phenotype correlation.

The heritable MEN tumors have important characteristics that contrast with those of sporadic endocrine tumors: genetic origin and transmission; precursor hyperplasias that predispose to younger clinical presentations and earlier diagnosis; multiplicity and multicentricity of tumor involvement (90%, 70%, and 100% of insulin-, gastrin-, and calcitonin-secreting tumors, respectively, vs. 10%, 40%, and 10% in their sporadic counterparts); a clinicopathologic spectrum with early, occult hyperplasia developing into later, symptomatic tumor; and, to some extent, more malignant biologic behavior of some of the tumors—MTC, enteropancreatic, and carcinoid in some families.

Generally, there is no overlap between MEN1 and MEN2. However, Frank-Raue et al. [8] and Scillitani et al. [9] have each reported a family with the coexistence of these syndromes and mutations of MEN1 and MEN2 genes. Furthermore, rare, isolated, mutation-negative cases that shared tumors from each syndrome have been reported [10,11].

MEN TYPE 1

This is a syndrome of the three Ps—pituitary, parathyroid, and pancreas. Principal organ involvement is outlined in Table 9.1. Differences in penetrance are considered reflections of the various family characteristics, ages, and years of the studies. MEN1 typically presents after the first decade, with most symptoms developing in the third (women) and fourth (men) decades. The presenting symptoms in an older series of 52 patients were associated with ulcer in 40%, hypoglycemia in 31%, hyperparathyroidism in 15%, and diarrhea and pituitary disease in 6% [12].

Screening

A comprehensive family history (an inexpensive process) and DNA analysis for the MEN1 mutation (expensive) should be pursued in patients having component tumor presentation at a young age, tumor multifocality, having two or more of its component tumors, or known to have heritable risk for MEN1. Genetic counselors are very helpful in this process. Sources and costs of mutation analyses can be found at www.geneclinics.org. Several benefits accrue to mutation-positive patients: clinical surveillance and care will intensify; operations for components such as multiglandular parathyroid disease and multifocal enteropancreatic tumors will differ from those in sporadic patients; and the mandatory case finding in at-risk primary relatives will be simplified (i.e., need to check for one known mutation only). Mutation-negative patients gain emotional reassurance and economic benefit because further clinical testing is not needed. Unfortunately, a mutation is not found in up to 30% of probands in known MEN1 families [8]. Screening in these families must revert to annual measurements of ionized calcium, parathyroid hormone (PTH), gastrin, and prolactin [13] and the recommended abdominal magnetic resonance imaging (MRI) every 2 years. Clinical expression generally occurs after age 10, but the authors recommend that screening begin at age 5 because of reports of prolactinoma in a 5-year-old [14] and insulinoma in a 6-year-old [15].

False-negative mutation screening test results may occur in individual patients within mutation-known families at "guesstimated" frequencies [15]. Analysis of a

second separate sample is recommended to reduce the risk of missing an affected to 0.25%. Thus far, false-positive mutation test results have not been reported, and the author is aware of no estimates of administrative, sampling, or reference laboratory errors.

Patients with three other diseases should have mutation testing or screening for MEN1: approximately 33% of patients with the Zollinger-Ellison syndrome (ZES) have MEN1; 4% to 10% of patients with insulinoma have the syndrome [16–18]; in familial hyperparathyroidism 14% to 16% have MEN1; and in those younger than age 40 thought to have sporadic hyperparathyroidism the prevalence of MEN1 has been estimated at 13%.

Enteropancreatic Disease

Enteropancreatic tumors are present in up to 75% of patients with MEN1. They are generally multicentric and found in the gastric antrum, pancreas, and duodenal submucosa (particularly gastrinomas). Occult malignant disease is present in one-half of these patients by middle age [19]. Most secrete one hormone (see Table 9.1) that produces a distinct clinical syndrome; occasionally, multiple hormones are secreted. Gastrin, insulin, chromogranin A, and pancreatic polypeptide are hormones that may be secreted by these tumors in significant amounts to be used in annual screening as markers for the enteropancreatic tumors.

Gastrin-Secreting Tumors

Gastrin-secreting tumors are the most common functioning tumors and have the greatest malignant potential. Most are small, multiple, and within the pancreas and duodenum; about 90% have duodenal components. Half have metastasized before the diagnosis is made [19]. The clinical syndrome caused by excess gastrin secretion—ZES—does not differ between MEN1 and sporadic tumors [12,20]. Excess gastrin causes secretory diarrhea and ulcerations in the esophagus, stomach, and duodenum–jejunum, producing abdominal pain. In an early clinical report, 50% of patients exhibited multifocal peptic ulcers and esophagitis, and 13% had watery diarrhea [12].

Diagnosis

Measurement of basal gastrin and hourly gastric acid output is mandatory. High gastrin concentrations (generally above 200 pg/ml) and gastric acid secretion are the hallmarks of ZES in patients with no history of acid-reducing medications or operations. Basal gastric acid secretion that exceeds 15 mEq/hr is found in 68% to 97%. These tests will exclude 88% to 96% of patients who have ordinary duodenal ulcers [21]. To distinguish patients with ZES symptoms and minimally elevated basal gastrin values, a secretin test using 2 U/kg is advised. Gastrin increases of 200 pg/ml or more are diagnostic for ZES, with no false-positive responses and only occasional false-negative responses reported [22,23]. Protein pump inhibitors must be stopped for at least 1 week before the secretin test. History is an inexpensive way to exclude other causes of high gastrin such as retained gastric antrum, gastric outlet obstruction, and renal failure.

If operation is planned, favored localization studies are somatostatin receptor scintigraphy (SRS) with octreotide and endoscopic ultrasound (EUS). Both have sensitivities in the 80% to 90% range, with the warning that SRS detects only 30% to 75% of tumors smaller than 1.5 cm [24,25]. However, SRS has the advantage of simultaneous detection of primary pancreatic tumors and liver and other metastases. Some also use MRI and computed tomography (CT) to exclude metastatic disease that would preclude surgical intervention; however, these modalities are insensitive for the detection of smaller tumors, localizing

only 26% and 31% of insulinomas and gastrinomas, respectively [26,27]. EUS has reported sensitivity of 93% and specificity of 95% in the localization of intrapancreatic lesions [28]. In one case–control study of gastrinoma patients, EUS was 83% accurate, missing tumors in 4 and predicting nonexistent tumors in 2 of 36 patients (i.e., false-positive result) [29]. It was cost-effective, reducing localization costs by 50%. If these procedures are not successful, comparable sensitivity is possible with the more expensive and time-consuming percutaneous transhepatic transvenous sampling or with venous sampling for hormone measurement after arterial injection of secretagogue. Hepatic angiography is an excellent way to demonstrate hepatic metastases.

Treatment

Proton pump inhibitors or occasionally H_2 receptor blockers and somatostatin analogues for hormones other than gastrin effectively prevent morbidity in most patients [19].

Operations, when done, should include distal pancreatectomy, intraoperative ultrasonography and palpation (to delineate smaller tumors), enucleation of tumors in the head of the pancreas, exploratory duodenotomy with removal of smaller tumors and carcinoids, and lymphadenectomy around the celiac trunk and hepatic ligament. Indications for operation in MEN are evolving. All clinicians agree with surgery for failed medical treatment or palliation of advanced disease. Otherwise, controversy exists regarding the surgical management of these patients. We do not know whether earlier surgery will reduce death from cancer without increasing morbidity; we lack long-term randomized studies of patients treated with no operation versus a standardized operation that compare survival and operative morbidity. Conservatives cite the 100% survivorship over 15 years in patients with tumors smaller than 1.5 cm who have not had operation [30]. By contrast, a study reporting no operative cure for gastrinomas larger than 2.5 cm [31] weakens arguments for waiting to remove tumors until they reach 3 cm. There is no correlation between the size of the primary tumor and the incidence of regional or distant metastases as shown by the isolated discovery of metastasis associated with a 3-mm primary tumor [32]. In their review of 34 articles on this subject, Schreinemakers et al. [33] stated: "Gastrinoma tumors > 3 cm were associated with a worse outcome. Biochemical cure was observed in 64–77% when all gastrinomas or gastrinomas >1 cm were operated, compared to 0% when tumors > 2.5 cm were operated." In gastrinoma patients, the presence of hepatic metastases is a major factor associated with poor prognosis. Because the incidence of liver metastases is directly related to size of the primary tumor (4% with tumors <1 cm vs. 61% in tumors >3 cm), operations at earlier stages seem best advised. Fraker et al. [34] found an eightfold reduction in hepatic metastases when they compared patients with large tumors who were managed medically to those with smaller tumors who were operated with intent to cure.

Less conservative clinicians argue that patients should have operations because of the difficulty in predicting which primary tumors will metastasize and when they will do so. The University of Michigan group has operated on about 15 presymptomatic patients. Their intervention includes distal pancreatectomy, intraoperative ultrasonography, palpation and removal of tumors localized in the pancreatic head, duodenal submucosa, and antrum, as well as dissection of lymph nodes along the celiac axis and hepatic ligament. All 15 patients continue to have normal gastrin levels, and only 1 patient has developed diabetes mellitus [35]. Skogseid et al. [36] have complementary results. The follow-up is short in both studies, but the early results suggest need for a larger, longer, randomized study.

For patients with metastatic disease the therapeutic options include chemoembolization, chemotherapy, alpha interferon, peptide radioreceptor therapies, and somatostatin analogues. Recent reports about patients with advanced pancreatic neuroendocrine tumors (functional and nonfunctional with limited MEN1 participants) treated with sunitinib malate or everolimus have shown improved progression-free survival and objective response rates with treatment compared to placebo [37,38]. Further discussion is not within the scope of this text.

Insulin-Secreting and Other Tumor Types

Between 10% and 30% of enteropancreatic tumors secrete insulin. The youngest patient studied was aged 6. Insulinoma is a more common functioning tumor in patients younger than 25. Most tumors are pure insulin secretors; some produce both insulin and gastrin [39]. Both types cause hypoglycemia.

Diagnosis

The diagnosis is based on finding simultaneous fasting serum glucose values below 45 mg/dl and inappropriately high insulin concentrations (>10 mU/ml). Typical requirements for this study are a 72-hour fast with measurement of plasma glucose and insulin every 6 hours or measurement of insulin and C-peptide before and during induced hypoglycemia [37–40].

Treatment

Operation is recommended in all insulinoma patients. Pre- and operative tumor localization may be done with ultrasonography, CT, endoscopic ultrasonography, and intraoperative ultrasonography. The initial therapy for insulinoma is a distal pancreatectomy, which should remove about 85% of the gland [18,41]. This procedure is favored for three reasons. First, multicentric insulin-secreting tissue is present in over 90% of patients. Second, 5% to 15% of the tumors are malignant. Third, endocrine and exocrine insufficiency is reduced significantly with distal compared to total pancreatectomy. Intraoperative monitoring of glucose is helpful in determining the degree of pancreatectomy. More than 90% of patients are cured by such operations. If hypoglycemia persists following operation, diazoxide may be used; if metastatic disease is present, streptozocin, dacarbazine, or somatostatin analogues may be effective in decreasing hypoglycemia [42].

A glucagon-secreting tumor without the necrolysis syndrome has been reported in a euglycemic woman, and hyperglucagonemia has been reported in five of six patients studied [14,43]. Vasoactive intestinal polypeptide and other hormones have been found (see Table 9.1). Malignant behavior is rare. These tumors are resected when not controlled by medication.

Parathyroid Disease

Multigland, asymmetric, hyperplastic parathyroid disease is the most penetrant and generally earliest manifestation of MEN1; it affects 87% to 97% of patients and is detected in the second and third decades [19]. Ectopic gland locations such as thymus, thyroid, and paraesophageal are common, and supernumerary glands occur. MEN1 is rare among cases of hyperparathyroidism. The differential diagnosis includes familial hyperparathyroidism alone and benign familial hypocalciuric hypercalcemia. Although it is commonly asymptomatic, the usual symptoms or signs of hyperparathyroidism may occur including severe osteopenia in 40% [44]. Thus, bone mineral density measurements are necessary for the assessment and follow-up of patients.

Diagnosis

Diagnosis is established by finding high concentrations of serum calcium and PTH. Because of possible benign familial hypocalciuric hypercalcemia, calcium/creatinine clearance ratios should be calculated. There is general agreement

that multiple parathyroid glands are affected with a disease spectrum from hyperplasia of all glands through combinations of hyperplastic, adenomatous, and ectopically located disease. Parathyroid cancer occurs, but is rare [45]. Such multiplicity requires that all glands be identified at initial surgery; therefore, preoperative imaging studies are unnecessary and not cost-effective. We think that parathyroid operations in MEN1 patients should be done only by very experienced endocrine surgeons and that patients must understand before operation that, because of gland multifocality, recurrence is common, that reoperation is possible, and that hypoparathyroidism is possible.

Treatment

Indications for and goals of operation are similar to those in sporadic disease but include additions to favor ease of second surgery for recurrent disease. In patients having simultaneous occurrence of both hyperparathyroidism and pancreatic tumors, the parathyroidectomy should occur first. This will avoid the risk of major hypercalcemia should immobilization occur following the pancreatic surgery, and, in those with gastrin-secreting tumors, a reduction in serum calcium may lower both gastrin and gastric acid secretion. Major surgical options are subtotal parathyroidectomy (>3.5 glands) with remnant gland marking or total parathyroidectomy with auto transplantation. Randomized trials of these different operations have not been done. Our general impression suggests that the former operation leads to greater rates of persistence or recurrence (8%–12%) and does not reduce the frequency of hypoparathyroidism. In subtotal parathyroidectomy with transcervical thymectomy, there is preservation of 30 to 50 mg of identified tissue. Total parathyroidectomy with autologous autotransplantation of tissue to an ectopic site appears to be gaining favor. It reduces early recurrence rates, but hyperfunctioning autotransplanted grafts do cause late recurrence and autograft failure leads to hypoparathyroidism in 1% to 2%. Hypoparathyroidism occurs with either operation; therefore, cryopreservation of parathyroid tissue is strongly advised [46,47]. In selected cases, alcohol ablation of parathyroid tissue may be used to treat recurrence when additional glands are successfully localized. Difficult recurrent hypercalcemia, osteoporosis, or renal lithiasis may be treated with bisphosphonates. Faggiano et al. [48] reported treatment with depot somatostatin analogue octreotide normalized serum calcium in 75% of eight treated patients.

The author agrees with the suggestion by Ferolla et al. [49] that thymectomy be done during parathyroidectomy in MEN1 patients as ectopic glands are often in the thymus, and 8 of 180 MEN1 cases in the Italian registry had malignant thymic carcinoid tumors (with subsequent death or metastases in 50%).

Pituitary Disease

The prevalence of pituitary disease in MEN1 ranges from 18% (clinical findings) to 94% (autopsy results), and it is a presenting complaint in 4% of cases [12,50,51]. Tumor types are shown in Table 9.1. The pathologic spectrum ranges from hyperplasia through adenoma to carcinoma (rare). In early series, tumors were macroadenomas. Presently, they are smaller because of early screening. Prolactin-secreting tumors are most common—up to 60%—and often are resistant to dopaminergic agents. A prolactin-secreting macroadenoma has been reported in a 5-year-old child [14]. A rare phenotype, the Burin variant, manifests with prolactinoma and hyperparathyroidism [52]. The symptoms, signs, diagnosis, and treatment of the pituitary tumors are similar to those of sporadic disease. Long-term follow-up for the pituitary includes examination, annual measurement of prolactin and insulin-like growth factor, and a pituitary MRI beginning at age 20 and continuing every 2 years.

Associated Diseases

Carcinoid tumors occur in up to 23% of patients [53–55]. The natural history of such lesions in MEN1 is sparse. Most tumors do not hypersecrete, so symptoms are rare and late. CT and MRI are used for screening and follow-up. Gastric enterochromaffin-like cell carcinoids are common—found in 23% of patients and in a background of universal enterochrommafin-like (ECL) cell proliferative changes [55]. It is proposed that genetic changes in MEN1 patients make ECL cells more sensitive to the proliferative effect of gastrin. Because of the possibility of malignant change in these tumors and observation of local metastases, even though survival is often great, patients are advised to have regular surveillance gastroscopies and biopsy of the mucosal lesions with removal of the carcinoid tumors.

Multiple facial angiofibromas are present in 88% and collagenomas in 72% [56]. Within affected families, they provide an excellent marker of MEN1. Adrenocortical abnormalities occur in up to 40%. Most are benign adenomas, but there is a variable pathologic and clinical spectrum. Cutaneous and visceral lipomas and uterine leiomyomas occur in about 10% of patients and are treated symptomatically.

MEN TYPE 2

The types and incidence of principle organ involvement in patients with MEN2 are shown in Table 9.1. Precursor stages exist for all components: C-cell hyperplasia (CCH) precedes MTC; diffuse or nodular adrenomedullary hyperplasia precedes P; and occult, normocalcemic parathyroid hyperplasia is observed [57–59]. More than 1,000 kindreds are known. Previously, asynchronous clinical manifestations led to discovery beginning in the third decade. Now, almost instant detection of asymptomatic affected babies or presymptomatic children occurs because of identification of RET codon mutations or high concentrations of plasma calcitonin, the hormone marker for CCH or MTC.

MEN2A patients have a normal phenotype and parathyroid disease. MEN2B patients have an abnormal phenotype that is easily recognized on physical examination; their MTC causes greater morbidity and mortality than those with MEN2A; and they have no parathyroid disease. So, in 1975 we named this group MEN2B [60]. The main features are well established [61,62]. Patients have a marfanoid habitus with excessive limb length, loose-jointedness, scoliosis, anterior chest deformities, and mucosal ganglioneuromas, but no ectopia lentis and cardiovascular abnormalities of the Marfan syndrome. There may be associated local peroneal to diffuse muscle weakness. The diffuse ganglioneuromatosis may present as yellow or white nodules of the tarsal plates of the eyes, associated with thickened corneal nerve fibers and pink, yellow, or translucent hemispherical nodules studding the tip and anterior third of the tongue, elongated projections posterior to each orolabial commissure, and nodules within the lips. Functionally, alimentary ganglioneuromatosis produces dysphagia, constipation, diarrhea, megacolon, and diverticulosis.

Screening

Testing for RET mutations in those at risk for MEN2 is the gold standard in this syndrome. It has replaced, but not eliminated, calcitonin (iCT) stimulation tests for case finding [63]. Current sources of mutation analyses can be found at www.geneclinics.org. This is cost-effective endocrinology at its finest. For less than $1,000, those with a mutation may be advised to undergo thyroidectomy, as 95% will develop MTC. Skinner et al. [64] have just reported an 88% cure rate for 50 consecutive patients having prophylactic thyroidectomy for MEN2A at age 19 or younger based on identification of RET mutations. Most importantly, patients

with two negative test results as well as their successors will require no further testing. However, there are important concerns about the testing. To avoid failed diagnosis, when an initial result is negative, a repeat test of a separate sample is necessary. There is an estimated 5% false-negative error rate in sample testing that is thought to be caused by mislabeled samples, or failed identification of known or unrecognized new mutations. A repeat test should reduce this "miss" rate to 0.25%. It will not eliminate the possibility that a new or unknown mutation has caused the problem. When that possibility is strong, an iCT measurement after stimulation is recommended in those at risk. False-positive RET testing results have been reported, even with repeat samples; one group has reported 3.4% of samples gave false-positive results [65]. Perhaps the tests were wrong; more probably, some carriers need decades to develop a second mutation that causes development of MTC, and some may never develop it.

All patients with MTC should be tested. Among patients assumed to have sporadic disease, the chance of being an index case with hereditable MEN2 is 5.8%, with a range up to 24% [66]. In primary relatives of those with positive RET mutations, the individual risk is 50%. Among all patients with P, 4% to 8% will be index cases for MEN2 [66]. Neumann et al. [67] did mutational analysis among 271 patients presumed to have sporadic P. Although 24% had mutations suggesting von Hippel-Lindau disease, the pheochromocytoma–paraganglioma syndrome, and MEN, only 4.8% were found to have MEN2 [56]. Among patients with Hirschsprung disease, RET mutations were found in about 50% [19]. No evidence suggests that screening patients with familial hyperparathyroidism is cost-effective.

Tests based on iCT measurement continue to have a role in three populations. First is the 2% to 5% of known MEN2 kindreds in whom a mutation has not been identified [68]. Second is cases in which FMTC is possible based on family history, but RET analysis is negative. Third is patients who are being followed after thyroidectomy. The author favors stimulation studies with pentagastrin or short calcium infusion, with the warning that samples should be sent to reference laboratories having very sensitive assays that have been standardized in normal persons for the secretagogue being used. Stimulation should not be used when the basal iCT concentration is known to be high because calcitonin is a potent vasodilator and shock might result.

Medullary Thyroid Carcinoma

MTC in MEN2 originates in parafollicular or C cells (so called because of their synthesis and secretion of iCT). The tumor has a solid pattern with amyloid in the stroma and a high incidence of lymph node metastases—particularly in the central compartment of the neck. The MTC is bilateral, multicentric, and associated with CCH and is found in the lateral, upper, and middle lobe portions. When detected in young patients by mutation or iCT screening, it is generally occult. When detected clinically, generally after the second decade, the tumor presents as a mass with or without cervical metastases.

Diagnosis

Detection of an RET mutation establishes that the patient has the potential to develop tumor, has CCH, or may have MTC. If suspicion is strong and RET mutation studies are negative, the disease may be confirmed by finding high basal or secretagogue-stimulated iCT concentrations.

Treatment

DNA-based prophylactic total thyroidectomy is the gold standard for therapy in asymptomatic RET carriers. Patients with an MEN2 mutation or high iCT

concentrations suggesting CCH or MTC require total capsular thyroidectomy, cervicocentral lymphadenectomy, and functional lateral neck nodal dissection at early ages [13,69–71]. The latter reference elegantly outlines why cervical lymphadenectomy is mandatory; metastatic tumor was missed more than 50% of the time if the procedure was done only when nodes were palpable. The authors reported that patients having unilateral/bilateral MTC had positive nodes as follows: central, 88%/78%; ipsilateral, 81%/71%; and contralateral, 44%/49%. When operated by a skilled surgical team, the incidence of vocal cord paralysis, hypoparathyroidism, and anesthetic and esthetic complications is low. Dralle et al. [72] suggested RET carriers are unlikely to benefit from prophylactic central node dissection during initial operation unless they have high basal iCT because they found no metastases in those who had normal basal and increased stimulated iCT values preoperatively.

Early thyroidectomy has lowered the mortality in hereditary MTC to below 5% with reported rates of 1.5% for patients operated following iCT screening detection, compared to 24% for those with symptomatic tumor [19,73]. In these early reports, no patients who had a total thyroidectomy in the first decade of life had residual tumor. This early observation has been extended by Skinner et al. [64] who reported 50 consecutive operations in MEN2A patients operated by age 19 based on positive RET mutation status. They reported that 88% were cured, with mean follow-up of 7 years, and that there was a "lower incidence of persistent recurrent disease in children who underwent thyroidectomy before age eight." In a retrospective meta-analysis of published reports of 256 pediatric MEN2 patients, Szinnai et al. [74] compared the results of early thyroidectomy (ages 1–5) and late thyroidectomy (ages 6–18). They found that early thyroidectomy prevented persistence or recurrence (0/9 patients) compared to late thyroidectomy (21/65 patients) attributable to removal of disease at earlier stages of demonstrated progressive malignant transformation.

Recommended ages for initial thyroidectomy in RET positive individuals are now being made based on correlations between genotype versus *average* phenotype behavior (malignant transformation, estimates of tumor virulence, presence of metastasis, and survivorship data) [69,75,76]. In some, the recommendations are based on good evidence and follow; in others, they may be based on small numbers. The authors base their "age of operation" decisions on the earliest reported age at which malignant transformation or metastasis occurs rather than *averages* in large series. We think removing malignant or premalignant tissue in children is more important than limiting the possibility of laryngeal nerve damage, hypoparathyroidism, and other complications. Thus, our recommendations are different. MEN2B patients with RET codon mutations 833, 918, and 922 have the most aggressive MTC with 10-year survivorship of 40% to 50%. Microscopic MTC has been found at 9 and 12 weeks and is common within the first year of life; metastases have been found at ages 3 and 12 months [77,78]. Thus, we recommend thyroidectomy beginning at age 3 months in MEN2B patients. Patients with MEN2 and RET codon mutation 634, the most common mutation, seem to have a medium risk level. Three patients with the 634 mutation deserve note because of atypical malignant transformation; one had invasive MTC at age 15 months; one had MTC by age 2 and one had metastases by age 5 [70,79,80]. Thus, the authors suggest it be done by age 2 and disagree with recommendations for thyroidectomy after age 5. In patients with MEN2A and RET codon mutations 603, 611, 618, 620, 630, 631, and 634, virulence and risk are medium. Thus, in these patients, it seems appropriate to defer operation to age 5 to 10 years. The lowest risk for early MTC and decreased survivorship is in those with 609, 768, 790, 791, 804, and 891 mutations. Operation in these patients may be deferred as

recommended—possibly to age 20 [81,82]. Once again, we urge that experienced, pediatric endocrine surgeons perform the operations in youngsters.

All patients will require levothyroxine replacement; if oral maintenance is difficult in children, weekly intramuscular therapy may be used. After operation, when patients have stable normal calcium concentrations, an iCT stimulation test should be done to evaluate outcome.

What should be done for patients who continue to have high iCT concentrations after primary surgery or who develop defined metastatic disease? Certainly those with bulky or invasive metastases in the neck deserve reoperation. The authors think those patients with aggressive tumors, those with RET genotypes known to be associated with increased tumor virulence, and those with rapidly increasing iCT doubling times should have aggressive attempts at tumor control. Barbet et al. who extended the 1984 work of Miyauchi et al. in thyroidectomized patients showed the importance of rapid iCT doubling times. Eight percent of those with iCT doubling times <6 months had 10-year survival; those with doubling times of 6 to 24 months had a 37% survival; and those with doubling times greater than 24 months had 100% survival [83,84].

Reoperation with curative intent has a place in the management of patients with persistent or recurrent MTC localized to the neck. For patients with no evidence for distant or directly visualized hepatic metastases (93% missed by conventional radiographic procedures), the Tissell extensive cervical microdissection operation done with curative intent is best. Fialkowski and Moley [85] have reported that 8 to 10 years after such operations, 26% of their patients have basal iCT levels of less than 10 pg/ml (they are probably "cured"), and 20.4% have levels less than 100 pg/ml.

Unfortunately, developing evidence suggests a majority of those with high postoperative iCT and no localizable disease with standard technology will be found to have hepatic metastases. Szavcsur et al. [86] demonstrated that 90% of 60 such patients have hepatic metastases demonstrated by hepatic angiography while MRI demonstrated disease in only 14%. Our personal experience suggests that hepatic metastases, although difficult, may be slow growing and not necessarily predictors of early death.

Until recently, there were no satisfactory nonsurgical means for treating metastases. TSH-suppressive doses of levothyroxine are not helpful. Treatment with radioiodine does not decrease recurrence or increase survivorship. External beam radiation may produce objective tumor decrement briefly in some [87], but, in general, the results are disappointing and survival is not increased. Conventional cytotoxic chemotherapies, as with doxorubicin or combination protocols, dacarbazine, and 5-fluorouracil, produce short response rates of 0% to 22%, do not prolong survival, and have difficult side effects [88]. Some have reported that treatments with metaiodobenzylguanidine (MIBG), which is stored in catecholamine vesicles, or a somatostatin analogue coupled with the beta radiation-emitting radioisotope 90-Y-DOTATOC have antitumor benefits [89]. Chemoembolization of liver metastases has been reported to reduce diarrhea episodes and diminish iCT [90].

More exciting are data about a group of drugs that inactivate the RET-activated tyrosine kinase receptors, which initiate or encourage thyroid cancer. At present, vandetanib is the most active of these agents. It is an orally bioavailable inhibitor of RET tyrosine kinase, vascular endothelial growth factor receptor and epidermal growth factor receptor signaling. As the MEN2 MTC is associated with mutations in the RET gene, the inhibition of tyrosine kinase activity causes decreased cell proliferation and metastasis and promotes apoptosis. Of 30 FMTC patients who received 300 mg of vandetanib daily, 20% had a partial response for mean

duration of 10.2 months, and an additional 53% experienced stable disease at greater than 24 months. In 25 of 30, there was a decrease in tumor size, and in 24 of 30 there was a 50% or greater decrease from baseline iCT concentrations [91]. Commonly reported side effects include diarrhea, rash, fatigue, headache, anorexia, nausea, hypertension, and QT interval prolongation. In a phase III, randomized, double-blind, placebo-controlled, multicenter study using vandetanib 300 mg in 331 patients with unresectable, locally advanced or metastatic hereditary or sporadic MTC, there was a 54% reduction in the rate of progression compared to placebo ($p = 0.0001$), and significant differences compared to placebo were also observed in secondary endpoints of objective response rate and disease control rate [92].

For those wishing a more intensive discussion of MTC and management issues, the authors suggest reference 4 by Kloos et al. that summarizes thoughts of the American Thyroid Association.

Pheochromocytoma

The prevalence of P in MEN2 ranges from 12% in young to 42%–100% in mature kindreds [93]. Codon 634 mutations are the most common leading to P and occur in 80% to 90% of patients with MEN2A. A progressive spectrum of pathology extends from bilateral diffuse and/or nodular adrenal medullary hyperplasia through large, multilobular P. Accessory adrenal gland involvement is occasional, and unilateral adrenal ganglioneuromas are reported in MEN2A and 2B [94,95]. Malignant P is reported in 4% of 300 MEN2 P patients studied by the Euromen group [96] to 29% in our early Mayo experience [58]. Because asynchrony (large ipsilateral tumor with contralateral, minimal disease) is common, detection of all disease at earlier stages may be difficult. The low-volume chromaffin tissue and asynchronous anatomical presentations in younger patients are often in asymptomatic and normotensive patients. The Ps in MEN2 are life threatening and may cause hyper- and hypotensive crises, cardiomyopathy, arrhythmia, complications of hypertension, and consequences of malignancy. Modigliani et al. [96] reported P as a direct cause of death in 8.3% of their 300 cases (in 40% of those the P was undiagnosed). Thus, patients having or at risk for P, those with only initial unilateral operations and those with metastases should be advised to avoid catecholamine-releasing medications such as pseudoephedrine (contained in about 40 over the counter (OTC) preparations) and similar agents or stressful procedures as they may trigger catecholamine crisis and death [97].

Diagnosis

MEN2 patients at risk should be screened for P annually, before or early in pregnancy, and before receiving general anesthesia. Machens et al. [98] suggested that screening start at the youngest age-related development of the tumor, which was age 10 for patients carrying mutations of codons 630, 634, and 918. We recommend age 5 for those with 918 mutations (MEN2B) as children ages 5 to 8 have been reported with bilateral adrenal medullary hyperplasia [99].

The best measurements are plasma-free metanephrine and normetanephrine because they have greater sensitivity and specificity than measurements of plasma or urinary epinephrine, norepinephrine, or their metabolites [100–103]. Anatomic localization is best done with CT or MRI (98% and 100% sensitivity, respectively); CT is more cost-effective. If CT shows unilateral enlargement only and bilateral tumors are assumed present, MIBG imaging can detect up to 25% of the functioning tumors missed by CT [100] and is helpful when seeking functional metastatic disease. Otherwise, MIBG should not be used as a primary means to diagnose P [104]. When available, 6-18F-fluorodopamine positron emission tomography may be used as it is more sensitive than MIBG or SRS [105].

Treatment

Once diagnosis is established, blockade with appropriate alpha- and beta-adrenergic blocking agents and glucocorticoid replacement therapy should start. For anatomically demonstrated bilateral disease, bilateral laparoscopic or open adrenalectomy has been the preferred operation. In unusual or extraordinary situations (i.e., commercial airline pilots), some have used unilateral laparoscopic so-called cortical sparing operations [106,107]. For so-called unilateral disease, many surgeons favor unilateral laparoscopic adrenalectomy.

The decision about initial bilateral versus unilateral adrenalectomy in MEN2 is complex and controversial. The authors favor initial bilateral total laparoscopic adrenalectomy for several reasons. (1) P may cause death. (2) The disease is always anatomically bilateral. (3) Tumors may present asynchronously—both anatomically and physiologically—and only 50% are symptomatic. (4) Adrenal medullary hyperplasias—unlikely diagnosed by common radiographic procedures—may cause hypertension. (5) A reported malignancy rate between 4% and 29% [58] and no knowledge as to size of primary tumor when metastasis occurs. (6) The failure of initial unilateral operations. In patients having an initial unilateral procedure, the contralateral gland commonly produces sufficient clinical disease to require operation within a few years. We have found reports of 565 patients having MEN2 and adrenalectomy for P. Of 565, 280 had initial bilateral adrenalectomy and 285 had initial unilateral adrenalectomy. Within a mean of 6.5 years, 80 of the 285 or 28% developed sufficient clinical findings to cause a completion adrenalectomy. It seems likely that more will fail with time. During the interval between operations, the patients have continued risk for the consequences of P, have been subjected to increased mutagenic radiation from repeated CT procedures, and have incurred the expense of these procedures and catecholamine or metabolite measurements—generally on an annual basis.

There is direct evidence from epidemiologic studies that organ doses from a single CT study (radiation dose range of 30–90 mSv) produce increased cancer risk. The evidence is reasonably convincing for adults and very convincing for children [108]. For a 25-year-old patient, one abdominal CT scan translates to a fivefold increase in the estimated lifetime risk of death from cancer. Adding a MIBG study contributes an additional 15 to 20 mSv. With annual studies, dose accumulation increases the risk. Thus, while trying to be helpful, we add more of the "mutational hits" suggested by Knudson [7].

The major reasons for not doing initial bilateral adrenalectomy are adrenal insufficiency and adrenal crisis. Deaths have been reported [109,110]. With mean follow-up of 14 years, deGraaf et al. reported that 32% of 28 patients with MEN2 who had bilateral adrenalectomy had adrenal crisis and one died. We recognize that patients require careful instruction and education by an endocrinologist on the care of adrenal insufficiency with emphasis on the need for adequate sodium intake, gluco- and mineralocorticoid therapy, and volume expansion and parenteral corticoids in emergencies. All should wear Medic-Alert identification, and we think patients benefit from participation in adrenal insufficiency support groups.

Patients with presumed sporadic or nonsyndromic P should be screened for germline mutations known to cause a pheochromocytoma/paraganglioma (P/P) syndrome. Before genetic test availability, we screened 44 patients who had presumed sporadic P for MTC using iCT measurement; 3 of 44 (7%) had MEN2 [111]. Mutation screens identify between 12.7% and 24% of so-called sporadic P patients as index cases in those with several entities including von Hippel-Lindau syndrome (VHL), MEN2, P/P syndromes type 1 (PP1 = SDHD) and type 4 (PP4 = SDHB), and neurofibromatosis type 1 (NF1) [112,113]. Studies by Neumann, Jimenez, Amar, and their respective colleagues [112,113] show the

percent of these mutations to be VHL (11.07/5.04/5.03); MEN2 (4.79/1.55/0.38); PP1 (3.72/0.77/4.05); and PP4 (6.38/6.97/4.42). With time, the high cost to detect such abnormalities should decrease. Meanwhile, to reduce cost, we encourage use of the clinical predictors and stepwise schemas suggested by Jimenez et al. Neumann et al. [112], and Gimenez-Roqueplo [114,115] to decide whom and how to screen. Sources for genetic tests may be found at www.genetests.org.

Parathyroid Disease

Clinical or anatomic evidence of parathyroid disease is present in 29% to 64% of patients with MEN2A. It is more common in patients with the 634 codon mutation, and the prevalence shows a high interfamilial variability [116]. In the patients with parathyroid disease, parathyroid hyperplasia is present in 84% and parathyroid adenoma(s) or combinations of both in 16%. Mild hypercalcemia is common. It is more often occult in younger MEN2A patients who often have normal ionized calcium and PTH concentrations and the discovery of minimal hyperplastic glands at the time of cervical exploration. Parathyroid disease is rare in MEN2B. Diagnosis is made by finding simultaneous high ionized or total calcium and iPTH concentrations.

Treatment

The indications for parathyroidectomy and the preferred operations are similar for patients with MEN2A and MEN1. Goals are to cure the disease, have minimal recurrence, and avoid hypoparathyroidism. Very experienced endocrine surgeons should do the operation, and cryopreservation of parathyroid tissue is advised. The major surgical options are subtotal parathyroidectomy or total parathyroidectomy with autotransplantation. Our general impression suggests that the former leads to greater rates of persistence or recurrence and does not reduce the incidence of hypoparathyroidism. Total parathyroidectomy with autologous autotransplantation of tissue to an ectopic site is gaining favor. It reduces recurrence rates. Uncommon autograft failure may produce hypoparathyroidism, and autografts have been reported to hyperfunction, requiring revision. Skinner et al. [119] reported excellent results in 50 patients with MEN2A, all of whom had removal of all parathyroid glands with placement of intramuscular autografts in the forearm or neck during initial total capsular thyroidectomy and centrocervical lymphadenectomy. At 1 year or more after parathyroidectomy, three patients (6%), who were aged 4, 4, and 6 years at surgery, had hypoparathyroidism requiring treatment, and 47 of 50 (94%) were normal. Thymectomy is not needed for carcinoid tumors; it may be necessary to find ectopically located glands. In patients with sporadic hyperparathyroidism, screening for MEN2 with either iCT measurement or mutation analysis is not warranted as the yield is low.

SHOULD PATIENTS WITH THYROID NODULES BE SCREENED FOR MTC?

A final issue is whether to screen patients with nodular thyroid disease for MTC with iCT measurement. Multiple groups in Europe have advocated this beginning with the initial report of Pacini and subsequent reports of others and their respective colleagues [118–122]. For convenience, we have joined and summarized these reports.

The prevalence of MTC detected in these studies (vide supra) was 0.57%, 1.37%, 0.38%, 1.12% and 0.40%. Fine needle aspiration (FNA) biopsies did not predict as many as 54% of MTCs. When compared to historical MTC series, the screened patients were found to have earlier or lesser stages of disease. Between 50% and 66% of postoperative iCT values were undetectable or sufficiently low to suggest "cure." In one series, additional RET screens found that 20% of the cases were new index cases to familial MEN2.

Recommendations regarding use of such screens are controversial. While agreeing that the use of iCT for screening may detect MTC at an earlier stage, that overall survival may be improved, and that such screening would be cost-effective in the US, the American Thyroid Association 2009 guidelines did not recommend such screening [123]. Guidelines from the American Association of Clinical Endocrinology and European Thyroid Association in 2010 stated that "measurement of basal serum iCT level may be a useful test in the initial evaluation of thyroid nodules" [124]. Arguments favoring screening are multiple and include the following. FNA biopsies for detection of MTC are insensitive, leading to delayed and/or inadequate initial surgery and unnecessary secondary operations. When compared to historical series, the predominately sporadic MTC found by screening is discovered at earlier stages. More than 50% of cases are "cured" and there should be an as yet unproved, increased survivorship. Increased cure will reduce the necessity of or morbidity from secondary surgeries. Identification of new families with MEN2 at early stages should lead to increased case finding and prolonged survivorship in larger numbers of patients.

Arguments against screening are as follows: variable sensitivity and specificity of iCT assays, which may make prediction of MTC difficult; the incidence of false-positive iCT, leading to unneeded operations; and the fact that high iCT may be found in other diseases. These include autoimmune thyroiditis (which on occasion may have increased CCH), rare cases of hyperparathyroidism, pseudohypoparathyroidism, hypergastrinemia, chronic renal failure, other neuroendocrine tumors, mastocytosis and, rarely, the ectopic production by other tumors. Finally, there is speculation that CCH may not progress to invasive malignancy in all cases.

The main argument against screening patients with nodules has been cost-ineffectiveness. The reports by Cheung et al. [125] and Borget et al. [126] appear to weaken this argument. They have calculated the cost to be $11,793 per life year saved or $9,000 to add 2.2 life years to each patient with a positive result. This places the cost-effectiveness within the same range as screens for breast and colon cancer. Adopting some of the following changes in screening protocols should increase cost-effectiveness: measure iCT only in well-standardized two-site immunometric assays that detect only monomeric iCT; reintroduce pentagastrin to the US for in use in or use short calcium infusion stimulation tests; measure iCT in only one postsecretagogue sample (in both tests the maximal stimulation generally occurs at 2 minutes) and omit a basal sample; screen only patients who have equivocal FNA results; eliminate those with autoimmune thyroiditis from screening; improve the sensitivity of FNA by using calcitonin immunostaining; and use clinical judgment to eliminate screens or interpret abnormal results in those with possible high iCT caused by other disease states. In summary, we think iCT screening should be done, with the changes in protocol suggested above, in patients having nodular thyroid disease.

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7. (2) **Knudson AG Jr, Strong LC.** Mutation and cancer: Neuroblastomas and pheochromocytoma. Am J Hum Genet 1972;24:514–532.

   An observational study that plotted the age of onset of familial compared with that of nonfamilial pheochromocytoma. Postulated that in hereditary neoplasms a first genetic mutation makes cells susceptible to a second somatic mutation that transforms the cell into a malignancy.

8. (3) **Frank-Raue K** et al. Coincidence of multiple endocrine neoplasia types 1 and 2: Mutations in the RET protoncogene and MEN1 tumor suppressor gene in a family presenting with recurrent primary hyperparathyroidism. J Clin Endocrinol Metab 2005;90:4063–4067.

9. (3) **Scillitani A** et al. Coincidence of mutations in RET and MEN1 genes in a large Italian family. Hormones 2008. Supplement 2. 11th international workshop on multiple endocrine neoplasia. P51, page 28.

10. (3) **Pasini B** et al. A case of medullary thyroid carcinoma, parathyroid focal hyperplasia and pancreatic neuroendocrine tumor without RET and MEN1 mutations. Hormones 2008. Supplement 2. 11th international workshop on multiple endocrine neoplasia. OP-RC-3, page 81.

11. (3) **Fraenkel M** et al. A patient with a rare combination of multiple endocrine neoplasia. Hormones 2008. Supplement 2. 11th international workshop on multiple endocrine neoplasia. OP-RC-1, page 80.

12. (3) **Ballard HS** et al. Familial multiple endocrine adenoma–peptic ulcer complex. Medicine (Baltimore) 1964;43:481–500.

    An early observational review of the expressions of disease in MEN1 patients and families who were diagnosed based on clinical presentations at Henry Ford Hospital.

13. (4) **Sizemore GW.** Multiple endocrine neoplasia. In: Becker KL, ed. Principles and practice of endocrinology and metabolism. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2000:1696.

    A textbook chapter on MEN that includes discussions of screening procedures.

14. (3) **Stratakis CA** et al. Pituitary macroadenoma in a 5-year old: An early expression of MEN1. J Clin Endocrinol Metab 2000;85:4776–4780.

    Case report about a child who had growth acceleration, acromegalic features, and the earliest morbidity noted in the 85 kindreds with 565 MEN1–affected members seen at the National Institutes of Health.

15. (4) **Marx SJ.** Multiple endocrine neoplasia type 1: Clinical and basic insights. Syllabus for the 11th Annual Meeting of the American Association of Clinical Endocrinologists, Chicago, IL, May 1–5, 2002:14.

    The syllabus notes provide information on the genetics and mutation analysis of patients with MEN1 from the institution caring for the most patients.

16. (4) **Malagelada JR** et al. Medical and surgical options in the management of patients with gastrinoma. Gastroenterology 1983;84:1524–1532.

    A review with recommendations for management of MEN1 patients with the ZES.

17. (3) **Marx SJ** et al. Family studies in patients with primary parathyroid hyperplasia. Am J Med 1977;62:698–706.

    Recommendations for management of primary parathyroid hyperplasia in patients with MEN1.

18. (3) **Rasbach DA** et al. Surgical management of hyperinsulinism in multiple endocrine neoplasia, type 1. Arch Surg 1985;120:584–589.

    A review of 30 patients with insulinoma and MEN1 with recommendations for surgical management.

19. (4) **Brandi ML** et al. Guidelines for diagnosis and therapy of MEN type 1 and type 2. J Clin Endocrinol Metab 2001;86:5658–5671.

    A consensus paper by international physicians specializing in treatment of MEN with data and guides for major management decisions.

20. (3) **Zollinger RM** et al. Thirty years' experience with gastrinoma. World J Surg 1984;8:427–435.

    An observational study that outlines the ZES perfectly and comments about its association with familial disease.

21. (4) **Jensen RT** et al. Zollinger-Ellison syndrome: Current concepts and management. Ann Intern Med 1983;98:59–75.

    A review summarizing diagnostic criteria for ZES.

22. (3) **Deveney CW** et al. The Zollinger-Ellison syndrome: 23 years later. Ann Surg 1978;188:384–393.

    An observational study that presents gastrin values in patients with ZES and demonstrates the importance of the secretin test in the differentiation of ZES patients from others.

23. (3) **McGuigan JE, Wolfe MM.** Secretin injection test in the diagnosis of gastrinoma. Gastroenterology 1980;79:1324.

    An observational summary of results with gastrin and the secretin test in ZES patients.

24. (2) **Shi W** et al. Localization of neuroendocrine tumors with (In-111) DPTA-octreotide scintigraphy (Octreoscan): A comparative study with CT and MR imaging. Q J Med 1998;91:295–301.

    An observational study that shows sensitivity and specificity of octreotide scintigraphy for pancreatic tumor localization compared with CT and MR.

25. (2) **Bansal R** et al. Cost effectiveness of EUS for preopertive localization of pancreatic endocrine tumors. Gastrointest Endosc 1999;49:19–25.

    In this case–control study of patients undergoing surgery for pancreatic neuroendocrine tumors, 36 patients who had preoperative EUS were matched to 36 previous patients who did not. The diagnostic sensitivity of EUS was 83% and accuracy was 89%. Such results allow for discontinuation of more expensive angiograms.

26. (3) **Vinik AI** et al. Transhepatic portal vein catheterization for localization of insulinomas: A ten-year experience. Surgery 1991;199:1–11.

    Observational comparison of angiography and CT for localization, demonstrating that angiography is more helpful for localizing insulinomas—44% localized with angiography compared with 26% for CT.

27. (3) **Vinik AI** et al. Transhepatic portal vein catheterization localization of sporadic and MEN gastrinomas: A ten-year experience. Surgery 1990;107:246–255.

    Observational comparison of angiography, CT, and transhepatic venous measurement of gastrin for localization. Demonstrated that transhepatic venous sampling with gastrin measurement was best at 50%, while angiography and CT were equally helpful for localizing gastrinomas at 29% and 31%, respectively.

28. (2) **Anderson MA** et al. Endoscopic ultrasound is high accurate and directs management in patients with neruoendocrine tumors of the pancreas. Am J Gastroenterology 2000;95:2271–2277.

    A prospective report of EUS in the diagnosis of 82 patients (30 with MEN1) with neuroendocrine tumors treated at the University of Michigan.

29. (3) **Vitale G** et al. Slow release lanreotide in combination with interferon-alpha 2b in the treatment of symptomatic advanced medullary thyroid carcinoma. J Clin Endocrinol Metab 2000;85:983–988.

    In this study of seven patients with metastatic MTC, combined therapy with lanreotide and interferon for 12 months reduced flushing and diarrhea significantly. It also produced least transient decrements in calcitonin, but it did not decrease tumor size or prolong life.

30. (2) **Norton JA** et al. Comparison of surgical results in patients with advanced and limited disease with multiple endocrine neoplasia type 1 and Zollinger-Ellison syndrome. Ann Surg 2001;234:495–505.

Fifty-six patients with MEN1 and ZES who had tumors larger than 2.5 cm had somewhat variable operations that did not provide a cure, suggesting that, perhaps, long waits before surgery are ill-advised.

31. (2) **Weber HC** et al. Determinants of metastatic rate and survival in patients with Zollinger-Ellison syndrome: A prospective long-term study. Gastroenterology 1995;108:1637–1649.

    Based on longer survivorship, the authors recommended operating on patients who are afflicted with tumors larger than 3 cm.

32. (2) **Lowney JK** et al. Pancreatic islet cell tumor metastasis in multiple endocrine neoplasia type 1: correlation with primary tumor size. Surgery 1998;124:1043–1048.

    The authors conclude that the size of primary tumors in MEN1 does not correlate with metastatic potential, so that size is not a good criterion for justifying exploration.

33. (4) **Schreinemakers JMJ** et al. Surgical treatment of pancreatic endocrine tumors in patients with multiple endocrine neoplasia type 1 syndrome. A systematic review. Hormones 2008. Supplement 2. 11th international workshop on multiple endocrine neoplasia syndromes. P 44, page 62.

34. (3) **Fraker DL** et al. Surgery in Zollinger-Ellison syndrome alters the natural history of gastrinoma. Ann Surg 1994;220:320–330.

35. (4) **Thompson NW.** Management of pancreatic endocrine tumors in patients with multiple endocrine neoplasia type 1. Surg Oncol Clin North Am 1998;7:881–891.

    The study gives a complete description of intraoperative procedures for this disease.

36. (3) **Skogseid B** et al. Surgery for asymptomatic pancreatic lesions in multiple endocrine neoplasia type 1. World J Surg 1996;20:872–876.

    A randomized study comparing results of similar operations between 8 presymptomatic and 12 symptomatic patients. Favorable results occurred in the presymptomatic (a 25% cure rate and no localized metastasis) versus the symptomatic (a 7% cure rate and metastasis in 33%).

37. (2) **Raymond E** et al. Sunitinib maleate for the treatment of pancreatic neuroendocrine tumors. N Engl J Med 2011;364:501–513.

38. (2) **Yao JC** et al. Everolimus for advanced pancreatic neuroendocrine turmors. N Engl J Med 2011;364:514–523.

39. (4) **Service FJ.** Clinical presentation and laboratory evaluation on hypoglycemic disorders in adults. In: Service FJ, ed. Hypoglycemic disorders. Boston, MA: GK Hall, 1983:73.

    Details evaluations for hypoglycemia.

40. (4) **Service FJ** et al. C-peptide suppression test for insulinoma. J Lab Clin Med 1977;90:180.

    Describes the C-peptide suppression test and shows results it provided in affected patients.

41. (3) **Demeure MJ** et al. Insulinomas associated with multiple endocrine neoplasia type 1: The need for a different surgical approach. Surgery 1991;110:998–1004.

    Results demonstrate favorable outcomes in patients with distal pancreatectomy.

42. (3) **Osei K, O'Dorisio TM.** The effects of a potent somatostatin analogue (SMS201-995) on serum glucose and gastro-entero-pancreatic hormones in a malignant insulinoma patient. Ann Intern Med 1985;103:223–225.

    Results of the study indicated reduced hypoglycemia in a patient having this treatment.

43. (3) **Croughs RJ** et al. Glucagonoma as part of the polyglandular adenoma syndrome. A J Med 1972;52:690–698.

    A case report suggesting that glucagonoma plays a role in the syndrome.

44. (3) **Burgess JR** et al. Osteoporosis in multiple endocrine neoplasia type 1: Severity, clinical significance, relationship to primary hyperparathyroidism, and response to parathyroidectomy. Arch Surg 1999;134:1119–1123.

    Report from an Australian group with great experience in MEN1. Twenty-nine patients had hyperparathyroidism; osteopenia was present in 41% and osteoporosis in 45%. In five patients with successful parathyroidectomy, results of sequential bone density studies showed it increased 5.2% in the femoral neck and 3.9% in the lumbar spine over 12 to 24 months.

45. (4) **Linas J** et al. MEN1 mutation caused bilateral parathyroid carcinomas. J Clin Endocrinol Metab 2006;93:2011–2024.

46. (2) **van Heerden JA** et al. Primary hyperparathyroidism in patients with multiple endocrine neoplasia syndromes. Arch Surg 1983;118:533–536. Hormones 2008. Supplement 2. 11th international workshop of multiple endocrine neoplasia. 2008, P46, page 63.

Forty-three patients with MEN were treated by subtotal parathyroidectomy. The cure rate was 93%, but 23% developed hypoparathyroidism. Because of this, the authors recommended cryopreservation of tissue for subsequent transplantation.

47. (2) **Lambert LA** et al. Surgical treatment of hyperparathyroidism in patients with multiple endocrine neoplasia type 1. Arch Surg 2005;140:374–382.

Results in 37 patients from the MD Anderson Cancer Center experience and a thoughtful review.

48. (2) **Faggiano A** et al. Effect of treatment with depot somatostatin analogue octreotide on primary hyperparathyroidism in MEN1 patients. Hormones 2008. Supplement 2. 11th international workshop on multiple endocrine neoplasia. P69, page 74.

Eight patients with MEN1 and hyperparathyroidism were treated with the somatostatin analogue; hypercalcemia was normalized in 75%.

49. (3) **Ferolla P** et al. Thymic neuroendocrine carcinoma (carcinoid) in multiple endocrine neoplasia type 1 syndrome: The Italian series. J Clin Endocrinol Metab 2005;90:2603–2609.

A summarized experience about Italian MEN1 patients with malignant thymic carcinoids. 3.1% of their 180 patients with familial MEN1 had the cancer, which was fatal or metastatic in 50%.

50. (2) **Burgess JR** et al. Spectrum of pituitary disease in multiple endocrine neoplasia type l: Clinical, biochemical and radiological features of pituitary disease in a large MEN1 kindred. J Clin Endocrinol Metab 1996;81:2642–2646.

A report of the spectrum of pituitary disease in 165 members of one kindred with MEN1: 19% were found to have pituitary disease. It was symptomatic in only 24%, suggesting that screening is needed for detection. The data supported the use of α-subunit, prolactin, and IGF-1 measurements for screening. One-third of prolactinomas did not respond to therapy with bromocriptine, suggesting less responsiveness than in sporadic tumors.

51. (3) **Majewski JT, Wilson SD.** The MEA-I syndrome: An all or none phenomenon? Surgery 1979;86:475–484.

This study adds more information about the penetrance of MEN1.

52. (3) **Petty EM** et al. Mapping of the gene for hereditary hyperparathyroidism and prolactinoma (MEN1 Burin) to chromosome 11q: Evidence for a founder effect in patients from Newfoundland. Am J Hum Genet 1994;54:1060–1066.

Details the Burin variant of MEN1, which has a predominance of prolactinoma and hyperparathyroidism.

53. (3) **Williams ED, Celestin LR.** The association of bronchial carcinoid and pluriglandular adenomatosis. Thorax 1962;17:20.

The first report of carcinoid tumors in MEN1.

54. (4) **Teh BT** et al. Clinopathologic studies of thymic carcinoids in multiple endocrine neoplasia type 1. Medicine 1997;76:21–29.

An excellent, thorough review of this subject.

55. (2) **Berna JJ** et al. A prospective study of gastric carcinoids and enterochrommafin-like (ECL) cell changes in multiple endocrine neoplasia type 1 and Zollinger-Ellison syndrome: Identification of risk factors. J Clin Endocrinol Metab 2008; 93:1582–1591.

A prospective study of 57 patients with MEN1 and high fasting gastrin using gastroscopy and multiple mucosal biopsies, which demonstrated advanced proliferative ECL changes in 53%, gastric nodules in 44%, and carcinoid tumors in 23%. The results emphasize the need for surveillance of such patients with the unstated implication of decreasing death in such patients.

56. (2) **Darling TN** et al. Multiple facial angiofibromas and collagenomas in patients with multiple endocrine neoplasia type 1. Arch Dermatol 1997;133:853–857.

In 32 patients with MEN1, facial angiofibromas were found in 88% and collagenomas in 72%. The results suggest these entities are excellent indicators of affected status.

57. (3) **Wolfe HJ** et al. C-cell hyperplasia preceding medullary thyroid carcinoma. N Engl J Med 1973;289:437–441.

First demonstration of the medullary carcinoma precursor lesion in two sisters with MEN2 and a comparison to the inhomogeneous spacing in normal persons. This provided the realization that bilateral total thyroidectomy would be needed even in those with nonpalpable lesions.

58. (3) **Carney JA** et al. Adrenal medullary disease in multiple endocrine neoplasia, type 2: Pheochromocytoma and its precursors. Am J Clin Pathol 1976;66:279–290.

This study documents the bilateral adrenal disease in the first 19 patients having adrenalectomy at Mayo Clinic with MEN2. This study outlines the stages of adrenal medullary hyperplasia, demonstrates that the disease presents asynchronously, and shows these Ps may be malignant.

59. (2) **Heath H II** et al. Preoperative diagnosis of occult parathyroid hyperplasia by calcium infusion in patients with multiple endocrine neoplasia, type 2a. J Clin Endocrinol Metab 1976;43:428–435.

A study of eight unaffected people, six normocalcemic patients with MEN2A, and seven patients with MEN2B. During calcium infusion, there was failure to suppress PTH secretion in patients with MEN2A disease, and at operation they had parathyroid hyperplasia. Those with MEN2B had PTH suppression and normal glands at operation. This work established that normocalcemic parathyroid hyperplasia could be diagnosed preoperatively in MEN2A and that MEN2B patients have normal parathyroid function.

60. (3) **Chong GC** et al. Medullary carcinoma of the thyroid gland. Cancer 1975;35:695–704.

This review of Mayo patients first suggested the terms MEN2A and MEN2B to distinguish patients with MEN2 with distinctive clinical findings. The survivorship data established that MTC in MEN2B patients was more virulent than in sporadic disease and, in turn, more virulent than that in MEN2A.

61. (3) **Carney JA** et al. Multiple endocrine neoplasia, type 2b. Pathobiol Annu 1978;8: 105–153.

This review of Mayo patients with MEN2B established the subtle phenotypic and pathologic features of the syndrome.

62. (3) **Dyck PJ** et al. Multiple endocrine neoplasia, type 2b: Phenotype recognition, neurologic features and their pathologic basis. Ann Neurol 1979;6:302–314.

This review of Mayo patients established the phenotypic, pathologic, physiologic, and neurologic features in MEN2B.

63. (4) **Lips CJM.** Clinical management of the multiple endocrine neoplasia syndrome: Results of a computerized opinion poll at the Sixth International Workshop on Multiple Endocrine Neoplasia and von Hippel-Lindau Disease. J Intern Med 1988;243:589.

Results of a survey about management of the diseases at an international MEN meeting.

64. (2) **Skinner MA** et al. Prophylactic thyroidectomy in multiple endocrine neoplasia type 2A. N Engl J Med 2005;353:1105–1113.

A prospective study of 50 consecutive patients aged 19 or younger with MEN2A identified by RET mutation who underwent total thyroidectomy. Forty-four of fifty patients or 88% seem cured by objective criteria with greater than 5-year follow-up.

65. (2) **Kebebew E** et al. Normal thyroid pathology in patients undergoing thyroidectomy for a finding of a RET gene germline mutation: A report of three cases and review of the literature. Thyroid 1999;9:127–131.

Summarizes three false-positive determinations in MEN germline mutations and reviews the literature on such results.

66. (2) **Neumann HPH** et al. Pheochromocytoma, multiple endocrine neoplasia type 2, and von Hippel-Lindau disease. N Engl J Med 1993;329:1531.

A report of the incidence of pheochromocytoma in various syndromes.

67. (2) **Neumann HPH** et al. Germ-Line mutations in nonsyndromic pheochromocytoma. N Engl J Med 2002;346:1159–1466.

Mutation screening in 271 patients with presumed sporadic pheochromocytoma.

68. (3) **Berndt J** et al. A new hot spot for mutations in the ret proto-oncogene causing familial medullary thyroid carcinoma and multiple endocrine neoplasia type 2A. J Clin Endocrinol Metab 1998;83:770.

69. (2) **Russell CF** et al. The surgical management of medullary thyroid carcinoma. Ann Surg 1983;197;42–48.

A review of the operative procedures, pathology, and status of 123 Mayo Clinic patients who had operation for MTC. The results suggested the need for central lymphadenectomy at initial surgery because of a finding that, when done, 50% of patients had metastasis. The study also showed that in patients who initially underwent surgery, there was no difference in results from those having modified radical and radical procedures.

70. (2) **Schellhaas E** et al. Prophylactic central neck dissection with total thyroidectomy in familial medullary thyroid cancer with codon 634 mutations is safe and results in high cure rates. Surgery 2009;146:906–912.

A report of results in 17 patients with RET 634 codon mutations who had thyroidectomy and cervicocentral lymphadenectomy for MTC. Three of seventeen patients had CCH and fourteen had invasive MTC. Two of seventeen had central node metastasis not shown on preoperative ultrasound determinations. One patient (5.9%) developed permanent hypoparathyroidism. The authors argue that because the majority of these patients have invasive MTC, which is not detected preoperatively, and the complication rate is low, central cervical lymphadenectomy should be performed with the initial thyroidectomy.

71. (4) **Cohen MS, Moley JF.** Surgical treatment of medullary thyroid carcinoma. J Intern Med 2003;253:616–626.

A minisymposium on surgical treatment based on the authors' extensive personal experience, review of the literature, and personal opinion.

72. (2) **Dralle H** et al. Optimizing time and extent of prophylactic surgery in hereditary MTC. S8.2 page 23. Hormones 2008. Supplement 2. 11th international workshop on multiple endocrine neoplasia. P06, page 34.

73. (2) **Telenius-Berg M** et al. Impact of screening on prognosis in the multiple endocrine type 2 syndromes: Natural history and treatment results in 105 patients. Henry Ford Hosp Med J 1984;32:225–231.

A large observational study of 12 Swedish families with MEN2A, with some data extending as far back as 1730. By comparing mortality results in patients found by pentagastrin screening with those who presented with symptoms, they found a 5-year postsurgical mortality rate from MTC of 1.5% in 68 patients discovered by screening versus 24% in those who presented with symptoms. The index case in the largest family led to 71 affected cases.

74. (2) **Szinnai G** et al. Review of multiple endocrine type 2a in children: Therapeutic results of early thyroidectomy and prognostic value of codon analysis. Pediatrics 2003;111:132–139.

A retrospective meta-analysis of 256 pediatric patients having thyroidectomy for MTC in MEN2A.

75. (3) **Machens A** et al. Early malignant progression of hereditary medullary thyroid cancer. N Engl J Med 2003;349:1517–1525.

A retrospective attempt to provide guidelines for timing of prophylactic thyroidectomy in RET gene mutation carriers based on pathologic results of thyroidectomy in 207 European patients with operation for C-cell disease.

76. (3) **Saad MF** et al. Medullary carcinoma of the thyroid: A study of the clinical features and prognostic factors in 161 patients. Medicine (Baltimore) 1984;63:319–342.

Reviewed the operative procedures, pathology, and survivorship of 161 patients having surgery at MD Anderson for MTC.

77. (4) **Unruh A** et al. Medullary thyroid carcinoma in a 2-month-old male with MEN2B and symptoms of pseudo-Hirschsprung disease: A case report. J Pediatr Surg 2007;42:1623–1626.

Report of a child with MEN2B phenotype (codon 918 mutation) who had total thyroidectomy at age 9 weeks with a finding of MTC.

78. (3) **Zenaty D** et al. Medullary thyroid carcinoma identified within the first year of life in children with hereditary multiple endocrine neoplasia type 2A (codon 634) and 2B (codon 918). Eur J Endocrinol 2009;160:807–813.

Reports six patients with MEN2A (3) and MEN2B (3) operated by 12 months. All had formed MTC, and in patients with MEN2B, metastases were found at 3 and 12 months. This suggests thyroidectomy should be done in MEN2B patients by 3 months. One MEN2A patient did develop hypoparathyroidism.

79. (2) **Modigliani E** et al. Prognostic factors for survival and for biochemical cure in medullary thyroid carcinoma: Results in 899 patients. The CETC Study Group. Groupe d'Étude des Tumeurs à Calcitonine. Clin Endocrinol (Oxford) 1998;48:265–273.

A review of the screening and operative results of the national French study group in MEN.

80. (3) **Gill JR** et al. Early presentation of metastatic medullary cancer in multiple endocrine neoplasia, type IIA: Implications for therapy. J Pediatr 1996;129:459–464.

Reports metastasis by age 5 years in a patient with a codon 634 mutation. Leads to a recommendation for early surgery in that group.

81. (2) **Machens A** et al. Advances in the management of hereditary medullary thyroid cancer. J Intern Med 2005;257:50–59.

A review of the EUROMEN group data centered on genotype–phenotype correlations in RET oncogene-diagnosed MEN patients with personal interpretations.

82. (2) **Yip L** et al. Multiple endocrine neoplasia type 2: Evaluation of the genotype-phenotype relationship. Arch Surg 2003;138:409–416.

A prospective study of genotype–phenotype relationships in 71 patients with MEN2.

83. (2) **Barbet J** et al. Prognostic impact of serum calcitonin and carcinoembryonic antigen doubling-times in patients with medullary thyroid carcinoma. J Clin Endocrinol Metab 2005;90:6077–6084.

A small observational study predicted survivorship in MTC is reduced in patients with rapid calcitonin doubling time.

84. (2) **Miyauchi A** et al. Relation of doubling-time of plasma calcitonin levels to prognosis and recurrence of medullary thyroid carcinoma. Ann Surg 1984;199;461–466.

A large, retrospective, observational study that assesses the predictive value of postoperative calcitonin doubling times on survivorship of patients with MTC.

85. (2) **Fialkowski E** et al. Long-term outcome of reoperations for medullary thyroid carcinoma. World J Sur 2008;32:754–765.

Results of a prospective study of the Tisell extensive cervical microdissection technique. "Of the 93 patients operated on for cure (44 with hereditary MTC, 49 with the sporadic form), 8- to 10-year follow-up data were available on 56. Four patients died of disease (4.3% of 93). Two died of unrelated causes, and were excluded from calcitonin outcome analysis. Fourteen patients of fifty-four (26.0%) have unstimulated calcitonin levels of less than 10 pg/ml at 8 to 10 years. Eleven additional patients (20.4%) have levels of less than 100 pg/ml. None of these 25 patients (46.4%) have radiologic recurrence." The operation had reasonable rates of morbidity and no mortality.

86. (2) **Szavcsur P** et al. Angiography-proven liver metastases explain low efficacy of lymph node dissections in medullary thyroid cancer patients. Eur J Surg Oncol 2005;31: 183–190.

In 60 thyroidectomized patients with continued high iCT, the authors demonstrated that hepatic angiography demonstrated metastases in 90% whereas MRI showed them in 14%. Of note is that such metastases were not found on direct examination or biopsy in three patients.

87. (2) **Simpson WJ** et al. Management of medullary carcinoma of the thyroid. Am J Surg 1982;144:420–422.

This study demonstrated a twofold increased survivorship period in those who underwent secondary external radiation.

88. (4) **B.audin E** et al. New therapeutic approaches to metastatic thyroid carcinoma. Lancet Oncol 2007;8:148–156.

A review.

89. (2) **Gao Z** et al. The role of combined imaging in metastatic medullary thyroid carcinoma. J Cancer Res Clin Oncol 2004;130:649–656.

Report of imaging capabilities and treatment possibilities for 131I/123I-MIBG in patients with metastatic MTC.

90. (2) **Fromigue J** et al. Review: Chemoembolization for liver metastases from medullary thyroid carcinoma. J Clin Endocrinol Metab 2006;91:2496–2499.

Reports results from treatment of 12 patients with MTC metastatic to liver who were treated with chemoembolization.

91. (1) **Wells SA** et al. Vandetanib for the treatment of patients with locally advanced or metastatic hereditary medullary thyroid cancer. J Clin Oncol 2010;28:1–6.

A prospective study as described in the text.

92. (1) **Wells SA** et al. Vandetanib in locally advanced or metastatic medullary thyroid cancer: A randomized, double-blind phase III trial (ZETA). Presented at: 46th ASCO Annual Meeting, June 4–June 8, 2010; Chicago, IL. Abs 5503. Summary information provided by AstraZeneca LP.

93. (3) **Howe JR** et al. Prevalence of pheochromocytoma and hyperparathyroidism in multiple endocrine neoplasia type 2A: Results of long-term follow-up. Surgery 1993;114: 1070–1077.

These authors conclude that the penetrance of pheochromocytoma and hyperparathyroidism is variable in different kindreds with MEN2A but that the overall prevalence of pheochromocytoma approximates 40% and that of hyperparathyroidism 35%.

94. (2) **Nguyen L** et al. Pheochromocytoma in multiple endocrine neoplasia type 2: A prospective study. Eur J Endocrinol 2001;144:37–44.

A prospective study of 87 French MEN RET codon mutation carriers, ages 0.8 to 29 years, who were screened with 24-hour urinary catecholamine determinations during a mean 7.6-year study. Fourteen of eighty-seven or 16% had pheochromocytoma. CT failed to identify 25% of tumors, and MIBG diagnosed 10 of 11 patients correctly.

95. (3) **Lora M** S et al. Adrenal ganglioneuromas in children with multiple endocrine neoplasia type 2: A report of two cases. J Clin Endocrinol Metab 2005;90(7):4383–4387.

Case reports of ganglioneuroma in children with MEN2A and MEN2B.

96. (3) **Modigliani E** et al. Pheochromocytoma in multiple endocrine neoplasia type 2: European study. J Inter Medicine 1995;238:363–367.

A review of the European consortium experience with MEN2.

97. (4) **Sizemore GW** et al. Pseudoephedrine-induced hypertensive crisis, cardiomyopathy and death in a patient with pheochromocytoma. Endocr Pract 2008;14:93–96.

Case report of a young mother who had an undiagnosed pheochromocytoma, took two medications containing pseudoephedrine, and died with hypertensive crisis and cardiomyopathy.

98. (2) **Machens A** et al. Codon-specific development of pheochromocytoma in multiple endocrine neoplasia type 2. J Clin Endocrinol Metab 2005;90:3999–4003.

A cohort study with mean observation period of 27 years measuring time to diagnosis of pheochromocytoma in 206 consecutive with RET mutations. Earliest age of manifestation for genotypes 918, 634, 618, and 620 was 22, 18, 29, and 39 years, respectively. They concluded that annual screening start at age 10 for those with mutations in codons 918, 634, and 630 and from age 20 in the rest.

99. (4) **Decker RA** et al. Evaluation of children with multiple endocrine neoplasia type 2B following thyroidectomy. J Pediatr Surg 1990;25:939–943.

Descriptions of two cases with early pheochromocytoma.

100. (2) **Eisenhofer G** et al. Plasma normetanephrine and metanephrine for detecting pheochromocytoma in Von Hippel-Lindau disease and multiple endocrine neoplasia type 2. N Engl J Med 1999;340:1872–1879.

A prospective comparison of the value of plasma normetanephrine and metanephrine compared to the other major measurements of plasma and urinary catecholamines and metabolites for the diagnosis of familial pheochromocytoma. It included nine patients with MEN2. All patients with MEN2 had high concentrations of plasma normetanephrine, and eight of nine had high concentrations of plasma metanephrine. In the whole series of 35 patients, the sensitivity of measurements of plasma normetanephrine and metanephrine for the detection of tumors was 97%, whereas the other biochemical tests had a sensitivity of only 47% to 74%. The high sensitivity of these measurements was accompanied by a high level of specificity (96%). In the authors' opinion, this was an elegant study.

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102. (2) **Lenders JW** et al. Biochemical diagnosis of pheochromocytoma: Which test is best? JAMA 2002;287:1427–1434.

A comparison of multiple types of catecholamine and metabolites for the detection of pheochromocytoma.

103. (4) **Lenders JWM** et al. Phaeochromocytoma. Lancet 2005;366:665–675.

A review article on pheochromocytoma.

104. (3) **Lev I** et al. Clinical use and utility of metaiodobenzylguanidine scintigraphy in pheochromocytoma diagnosis. Endocr Pract 2010;16:398–407.

A non-MEN retrospective study of 98 patients who had MIBG scintigraphy over 14 years at Cedars–Sinai medical center. The major benefit of this study is to confirm that physicians incorrectly use the test and to direct physicians away from such studies by demonstrating that

CT/MRI imaging is better and that MIBG scintigraphy has large numbers of false-negative and false-positive results.

105. (2) **Ilias I** et al. Comparison of 6-18-Fluorodopamine PET with ^{123}I-Metaiodobenzylguanidine and ^{111}In-Pentetreotide scintigraphy (SRS) in localization of nonmetastatic and metastatic pheochromocytoma. J Nucl Med 2008;49:1616–1619.

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107. (3) **Neumann HP** et al. Preserved adrenocortical function after Met 1999;84: 2608–2610.

Four patients with hereditary bilateral adrenal pheochromocytoma were treated by laparoscopic surgery in an organ-sparing fashion. Postoperatively, all patients had normal urinary excretion of epinephrine and norepinephrine and normal cortisol responses to intravenous ACTH.

108. (4) **Brenner DJ, Hall EJ.** Computed tomography—an increasing source of radiation exposure. N Engl J Med 2007;357:2277–2284.

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109. (3) **deGraaf JS** et al. Complications after bilateral adrenectomy for phaeochromocytoma in multiple endocrine neoplasia type2—a plea to conserve adrenal function. Eur J Surg 1999;165:843–846.

A retrospective review of 28 patients with MEN2 who had total adrenalectomy with mean follow-up of 14 years (1–26). "Nine patients (32%) had a total of 19 Addisonian crises that necessitated hospitalization. One patient died of an unrecognized Addisonian crisis."

110. (2) **Asari R** et al. Estimated risk of pheochromocytoma recurrence after adrenal-sparing surgery in patients with multiple endocrine neoplasia type 2A. Arch Surg 2006;141:1199–1205.

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did not vary significantly with respect to the nature of the mutation, but it showed a high interfamilial variability.

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118. (2) **Pacini F** et al. Routine measurement of serum calcitonin in nodular thyroid diseases allows the preoperative diagnosis of unsuspected sporadic medullary thyroid carcinoma. J Clin Endocrinol Metab 1994;78:826–829.

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119. (2) **Niccoli P** et al. Interest of routine measurement of serum calcitonin: Study in a large series of thyroidectomized patients. J Clin Endocrinol Metab 1997;82:338–341.

A prospective study of 1,167 patients with nodular thyroid disease using iCT measurement. All patients had thyroidectomy. Reported a prevalence of 1.37% for MTC of (16/1167). There were no false-positive iCT results. Fifty percent of 16 patients with microscopic MTC had postoperative iCT values suggesting possible "cure." MTC was not identified in 70% of 10 patients having FNA biopsy.

120. (2) **Vierhapper H** et al. Routine measurement of plasma calcitonin in nodular thyroid diseases. J Clin Endocrinol Metab 1997;82:1589–1593.

A prospective study on 1,062 patients with nodular thyroid disease having iCT measurement. Fourteen patients had basal or postpentagastrin iCT concentrations of greater than l00 pg/ml; one refused surgery; one had no C-cell disease; six had MTC. Reported a prevalence of 1.12% (12/1061) for MTC or CCH. Eighty percent of those with MTC had normal postoperative iCT suggesting "cure." Thirty-three percent of the reported FNA biopsies were negative for MTC.

121. (2) **Elisei R** et al. Serum calcitonin should be measured in all patients with thyroid nodules. J Clin Endocrinol Metab 2004;890:163–168.

A prospective study of 10,864 patients with nodular thyroid disease having iCT measurement. Recommended operation in those with pentagastrin-stimulated iCT greater than 60 pg/ml. Reported a prevalence of 0.40% (44/10,864) for MTC. Forty-three of forty-four had MTC in the previously biopsied nodule; in one, the MTC was in a smaller adjacent nodule. Clinical diagnoses in those operated were multinodular goiter, uninodular goiter, toxic multinodular goiter, autonomously functioning nodule, and autoimmune disease with nodule. Fifty-nine percent of postoperative patients who had no response to pentagastrin at a mean of 6.2 years are considered cured, and sixty-six percent of those with MTC had normal postoperative iCT suggesting "cure." FNA diagnoses were incorrect and missed MTC in 54% of patients. When compared to a historical group of MTC patients treated without iCT measurement for nodules, the group was found to have MTC at earlier or lesser stages. New RET mutations were found in 20% of the 40 MTC patients screened! The estimated cost of detecting 1 MTC case/250 patients was $12,500.

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A prospective study of 5,817 patients with nodular thyroid disease having iCT measurement. The positive predictive value for MTC of a basal iCT concentration greater than 20 pg/ml was only 23%; thus, if basal iCT exceeded 20 pg/ml, pentagastrin stimulation was done, and if iCT exceeded 100 pg/ml, the patient was thought to have MTC. In patients with basal iCT exceeding 100 pg/ml, the positive predictive value was 100%; in those with pentagastrin stimulated iCT greater than 100 pg/ml, the positive predictive value was 87%. Among 25 patients with high iCT, two declined operation. The reported prevalence was 0.38% (21/5,817) for MTC or CCH. Findings in the 23 cases operated were MTC in 15; CCH in 6; neither in 2. Sixty-six percent of those with MTC had normal postoperative iCT suggesting "cure." Fine-needle aspiration biopsy did not suggest MTC in 33% of the 15 with MTC. One index case of MEN2B was found with the screening.

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Decision tree model was constructed for United States patients with thyroid nodules to determine and compare the cost-effectiveness of screening versus no screening for MTC with iCT.

126. (4) **Borget I** et al. Editorial: Calcitonin determination in patients with nodular thyroid disease. J Clin Endocrinol Metab 2007;92:425–427.

An editorial, which discusses data from multiple studies and uses data from one to estimate cost-effectiveness of such screening.

10

Carcinoid Tumors

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DEFINITION

Neuroendocrine tumors are characterized by the production, storage, and secretion of polypeptides, biogenic amines, and, in some cases, hormones. Carcinoid tumors, first termed in the early 1900s by Oberndorfer, fall under this designation. Oberndorfer noted small tumors of the gastrointestinal (GI) tract that were more indolent than adenocarcinomas and similar to the multiple tumors initially found and described by Lubarsch at autopsy of two patients in 1888. He termed these tumors "karzinoide," or cancer-like. Carcinoid syndrome is an uncommon constellation of symptoms (<10%) of these tumors and is associated with diarrhea, flushing (usually facial), hypotension, wheezing, and/or edema. Nocturnal perspiration is also a common symptom, although not routinely listed.

ETIOLOGY

Carcinoid tumors arise from neuroendocrine cells and can be classified according to where they occur in the body. The location has classically been based on the embryonic divisions of the alimentary tract and is divided into foregut (lungs, bronchi, and stomach), midgut (small intestine, appendix, and proximal colon), and hindgut (distal colon, rectum, and genitourinary tract). Among the foregut tumors, those of the pulmonary system are thought to derive their origin from the Kulchitsky cells located within the mucosa. Within the stomach, the tumors arise from the enterochromaffin cells (ECs) and have been associated with hyperplasia secondary to hypergastrinemic states. Studies in humans taking proton pump inhibitor (PPI) have not borne out gastric hyperplasia. However, when higher-potency PPIs are used for long periods of time, gastrin levels rise as does chromogranin A; this is due to the enterochromaffin-like (ECL) cells from the stomach.

An association between gastric carcinoid and Zollinger-Ellison with MEN1 syndrome (see below) is almost 100% [1]. Within the midgut tumors, those of the small intestine are thought to derive from hyperplasia of the serotonin-producing EC intraepithelial cells. Those tumors of the appendix presumptively arise from the subepithelial cells within the submucosa and lamina propria [2]. The reason for the hyperplasia is unknown. Of the hindgut tumors, colon carcinoids also

arise from the serotonin-producing cells of the epithelium, while in the rectum, the cells contain "glicentin" (100-amino-acid-residue peptide) and glucagon-like peptides [2]. The carcinoid syndrome is related to the release of those peptides and amines produced and stored within carcinoid tumors. Most symptoms are due to overproduction of tryptophan (especially the amine serotonin) or decreased elimination of the breakdown products. This is especially true of serotonin overproduction when carcinoid tumors metastasize to the liver.

EPIDEMIOLOGY

Carcinoid tumors are the most common type of neuroendocrine tumor in adults, accounting for approximately 55% of all new occurrences yearly affecting the GI tract. The overall occurrence is, however, still rare. Several studies have postulated the incidence to be 1 to 2 cases per 100,000 people [3,4]. The rate is similar for women, men, and among races, with slight variations based on the location and type of tumor expressed. Carcinoids occur across the age spectrum, with the peak incidence occurring between 50 and 70 years of age. Among carcinoid tumors, the most common site is the appendix followed by the rectum and then the ileum. Carcinoid is the most common tumor of the appendix and can account for up to 1/3 of small bowel neoplasms. In contrast, carcinoid tumors represent less than 2% of organ-specific tumors in the pulmonary, gastric, and colonic/rectal systems. Carcinoid syndrome occurs only in a minority of patients (<10%). The presence of this syndrome varies by site of tumor, as well as size and metastatic disease.

Pathology

As previously mentioned, carcinoid tumors are classified according to the different embryonic divisions of the GI tract (fore-, mid-, and hindguts). The individual cells are further divided as "typical" and "atypical," with typical cells classified as insular, trabecular, glandular, undifferentiated, and mixed [2,5]. Malignant versus benign is based on cellular histology as well as tumor size at surgery and site of primary occurrence. "Typical" pulmonary carcinoids are indolent and perihilar in location, with less than 15% metastasizing. In contrast, "atypical" carcinoids of the lung have a 30% to 50% incidence of metastases and are often more aggressive. They may secrete ACTH and result in Cushing syndrome. Of the gastric carcinoids, up to 75% are type 1 and associated with chronic atrophic gastritis, 10% to 15% type 2 and associated with Zollinger-Ellison syndrome, and the remainder sporadic or type 3. Most tumors are less than 1 cm in diameter, and types 1 and 2 have a more benign course. Those tumors greater than 2 cm (and type 3 tumors) are more likely to have metastatic disease at the time of diagnosis. Small bowel carcinoid is most commonly found in the ileum and often has multiple local sites of involvement. Unlike gastric tumors, size greater or less than 2 cm is a less reliable predictor of metastasis [6]. It has been observed that ileal tumors greater than 2 cm in size at surgery will metastasize locally or regionally 100% of the time. Within the appendix, most tumors occur at the tip and, most, are not associated with symptoms. Of appendiceal tumors, 95% are less than 1 cm; however, the 2-cm size delineation appears to correlate with both metastatic disease and the carcinoid syndrome [6]. Colonic tumors are often right sided with most occurring around the cecum. These tumors tend to be larger at diagnosis (5 cm) and more commonly associated with distant metastases, although less than 5% exhibit features of carcinoid syndrome. Rectal carcinoids occur predominantly (99%) within the zone defined as 4 to 13 cm above the dentate line, though the reason for this is not known. The majority (2/3) are less than 1 cm, but the association with metastatic disease and carcinoid syndrome is again defined by an absolute size of 2 cm.

Among all carcinoid tumors, more than 80% express somatostatin receptors. Of the five somatostatin receptor subtypes currently known to exist, types 2, 3, and 5 have been demonstrated on carcinoid tumors with type 2 predominating. As previously noted, carcinoid syndrome can be attributed to altered metabolism of tryptophan and subsequent conversion to serotonin or other breakdown products. Diarrhea, flushing, nocturnal perspiration, and cardiac manifestations (especially right-sided valve disease) have all been linked with this mechanism, while histamine from some gastric tumors may be associated with atypical flushing and pruritus as well as an increased occurrence of duodenal ulcers seen in this population. The syndrome usually is directly related to the ability of the tumor to secrete serotonin into the circulation system and bypass the breakdown that occurs in the liver [7]. As well, it can exceed the liver metabolism threshold resulting in high circulating serotonin concentrations. Evidence of this can be seen in the high association with hepatic metastases and the low incidence in patients with limited or local disease. One caveat to this syndrome is ovarian carcinoids; while rare, these are more often associated with this syndrome due to their direct vascular access. It is thought that the episodic secretion of serotonin and vasoactive peptides is due to the nonautonomous nature of the neuroendocrine tumors and the presence of somatostatin subtype 2 receptors on them.

DIAGNOSIS

Due to the indolent nature (thought to be due, in part, to the binding of endogenous somatostatin to the tumor somatostatin receptors subtype 2 [sst2]) and mostly occult presentation of most carcinoid neoplasms, the diagnosis is commonly not made until later in the course of the disease. Pulmonary involvement often manifests as cough, recurrent pneumonia, or hemoptysis. Gastric tumors are commonly found on routine endoscopies for symptoms of abdominal pain or gastritis, while those in the small bowel may present with signs of obstruction or nonspecific abdominal pain; some to the point regrettably of being labeled "psychosomatic" in origin. Appendiceal lesions commonly are found during routine appendectomies for appendicitis but may present with obstruction if located in the base rather than the tip of the appendix [8]. Abdominal pain without obstruction is a common complaint in colonic tumors as well as rectal pain with associated tumors. Intestinal bleeding is an uncommon presentation for both rectal and colonic tumors and is almost nonexistent with small bowel tumors. Rectal carcinoids are often found incidentally on routine colonoscopy or sigmoidoscopy. The carcinoid syndrome is often characteristic and can be the initial presentation for the underlying tumor [9].

Due to the heterogeneity of the presenting symptoms and indolent course of most carcinoids, there is very little consensus on the best imaging modality. The small size of most functioning tumors creates a problem for most diagnostic strategies. For carcinoid tumors with high-affinity somatostatin receptors, subtype 2, the OctreoScan has proven superior to other modalities with a sensitivity of 89% [7]. This scan allows localization of small lesions as well as defines the extent of distant metastases. Recently, the use of multiphase 68Ga-DOTATOC-PET/CT imaging has shown a benefit in influencing therapeutic options rather than either modality alone [10].

BIOMARKERS

Chromogranin A is a member of the family of polypeptides stored in the secretory granules of neuronal and neuroendocrine cells and their tumors. Circulating plasma chromogranin A levels are currently thought to be the best general "marker" for neuroendocrine tumors including carcinoids [11]. The development of a

human pancreastatin assay has promise in regard to a highly specific and sensitive assay for detection of liver tumor activity and follow-up of carcinoids and other neuroendocrine tumors that metastasize to the liver [12]. When carcinoid tumor is suspected, specific assay tests for the secretory product in question is the test of choice. Most commonly, this is a serum 5-hydroxyindoleactic acid (HIAA) level, although 24-hour urine collection can also be used [13]. However, it is important to note that, unless there is metastasis already present in the liver [14], 5-HIAA may not be appreciably elevated. The diagnosis of symptomatic carcinoid tumor may be extremely difficult, especially early on when these tumors are not autonomous and are under regulatory control (via somatostatin and its binding to the tumor membrane somatostatin receptors subtype 2). In this regard, we suggest the consideration for an OctreoScan be done at least one time early in the patient's course of diagnosis. As well, a serotonin plasma level is very sensitive for midgut carcinoids.

TREATMENT

The basis of treatment for most carcinoid tumors rests in tumor removal and symptomatic control. For pulmonary lesions, local resection has been shown to have a low rate of recurrence and a 5-year survival of 90%. Type 1 and 2 gastric carcinoids, less than 1 cm in size, are treated with local endoscopic resection with excellent prognosis. Type 3 lesions and those greater than 2 cm often necessitate a radical gastrectomy. Due to the more malignant nature and higher frequency of metastasis at diagnosis, small bowel tumors are often treated with small bowel and associated mesenteric dissection [15]. We support extirpation of small bowel primaries, regardless of metastatic status, since they can often obstruct. Simple tumors involving the appendix may be treated with appendectomy while lesions greater than 2 cm often receive a right hemicolectomy. Involvement of the colon commonly necessitates a total colectomy while rectal lesion less than 1 cm can receive local resection. However, rectal lesions greater than 2 cm should be referred for low anterior or abdominoperineal resection. In those patients who develop carcinoid-associated valvular heart disease, valve replacement can be of benefit although it is often associated with a high morbidity and mortality rate. For metastatic carcinoid in the liver, there is increasing literature to suggest that local resection and hepatic debulking should be offered as surgical adjuncts and improve survival [16,17].

As with the diagnosis of carcinoid tumors, the advent of somatostatin analogues (predominantly octreotide acetate, Sandostatin) has also lead to improved treatment and life expectancy of patients with these tumors [18,19]. Currently, Sandostatin LAR depot (monthly) and Lanreotide Depot (or SR) are the treatment of choice for controlling symptoms associated with these neoplasms and may also reduce the incidence of carcinoid heart disease. These congeners have been shown to reduce symptoms (including diarrhea and flushing) in 88% of patients as well as decrease 5-HIAA levels in up to 72%. They are also currently recommended for administration prior to surgery or chemotherapy in order to prevent the occurrence of carcinoid crisis. While Lanreotide Depot is not yet approved in the United States, it is widely used in Europe for neuroendocrine tumor therapy. The highly specific targeting Peptide Receptor Radio-Nuclide Therapy (P.R.R.N.T.) such as OctreoTher (y90-DOTA-modified octreotide, also termed y90-DOTATOC) is continuing to evolve and gain favor as a viable alternative therapy to chemotherapy [20]. Recent studies have shown both improvements in symptoms as well as stabilization or partial tumor regression in 65% to 70% of patients thus far treated over 3 years.

Although to a lesser extent than the somatostatin analogues, interferon-α has been shown to reduce both symptoms and tumor size. The high incidence of side effects can however be disabling and extract a significant toll.

Recent studies have shown that somatostatin used in conjunction with interferon-α is superior to either alone. Results from trials with chemotherapy have been disappointing; resulting in response rates of less than 20%. Currently, chemotherapy is only recommended when other therapies, especially surgery and octreotide, have failed. In general, a strongly positive photon emission tomography (PET) and weakly positive OctreoScan may predict better response to chemotherapy. Of symptomatic patients with hepatic involvement refractory to first line treatments, hepatic artery chemoembolization can result in a decrease in hormone levels and tumor size. Again, this procedure can be associated with significant morbidity including fever, nausea, and vomiting, especially when hepatic arteries are used for complete embolizations. Recently, there have been promising advances with the use of radiolabeled somatostatin analogues. Imhoff et al. showed improved survival, clinical, hormonal, and morphologic response to ^{90}yttrium-labeled tetraazacyclododecane-tetraacetic acid modified Tyr-octreotide ([^{90}Y-DOTA]-TOC) [21].

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   This retrospective case review is the largest published. The 8,305 cases were taken from the data banks and surveillance programs from the National Cancer Institute. The authors looked at overall incidence as well as individual tumor occurrence and survival data. They concluded that the overall incidence of carcinoids appears to have increased in the past 20 years and is most likely due to improved surveillance, data registries, and diagnostic technologies. The study also points out a 45.3% rate of metastatic disease at the time of diagnosis and an overall disease-specific 5-year survival of 50.4%.

4. (2) **Godwin JD**. Carcinoid tumors. An analysis of 2837 cases. Cancer 1975;36:560–569.

   This is a retrospective review of 2,837 cases from the files of the National Cancer Institute, which served as the initial cases used in reference 2 above. They report tumors found in the lung, ovary, biliary, and GI tract. Overall prevalence was highest in the appendix, rectum, and ileum. There was a low rate of concurrent or multiple neoplasms. Five-year survival ranged from 99% for appendiceal tumors to 33% for sigmoid colon tumors. Findings for this study were compared to other studies.

5. (2) **Arnold R**. Diagnosis and management of neuroendocrine tumors. In: 8th United European Gastroenterology Week. www.Medscape.com, 2001.

   This is a review (38 references) of the current pathologic classification system, a discussion of the pathology, diagnostic markers, imaging modalities, and current treatment options.

Diagnosis

6. (2) **Loftus JP, van Heerden JA**. Surgical management of gastrointestinal carcinoid tumors. Adv Surg 1995;28:317–336.

   This review (70 references) briefly discusses the history of gastrointestinal carcinoid tumors and their spectrum of disease. It is then followed by a complete discussion of the challenges surgeons face when confronted with these tumors. These challenges include accidentally discovered carcinoids, importance of size, diagnosis, and prognosis, as well as management including adjuvant chemotherapy.

7. (2) **Caplin ME** et al. Carcinoid tumour. Lancet 1998;352:799–805.

   This is a review (57 references) of the pathology of carcinoid tumors and a comprehensive discussion of the new treatment options available including octreotide for diagnosis and management. The authors conclude that there are currently better diagnostic tools and therapeutic

options for patients with carcinoid tumors. They also recommend that patients be treated with a multidisciplinary approach.

Pathology

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   This is a case review study of 154 patients who were surgically treated for gastrointestinal carcinoids at the Mayo Clinic between 1972 and 1982. The most frequent sites for tumor involvement were the ileum (43%), rectum (30%), and appendix (11%). They report that preoperative studies were of limited value except for endoscopy, and the overall mortality rate was 2.6%. There was also an unusually high incidence of metastasis from ileal primary tumors smaller than 1 cm (18%).

9. (2) **Maton PN**. The carcinoid syndrome. JAMA 1988;260:1602–1605.

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Treatment

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    Retrospective analysis of 66 patients with known or suspected neuroendocrine tumors (NET). The authors conclude that addition of multiphase CT in conjunction with PET adds to the treatment decision for patient with NET.

11. (2) **Baudin E** et al. Neuron-specific enolase and chromogranin A as markers of neuroendocrine tumors. Br J Cancer 1998;78(8):1102–1107.

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12. (2) **O'Dorisio TM** et al. Development of a highly sensitive and specific carboxy-terminal human pancreastatin assay to monitor neuroendocrine tumor behavior. Pancreas 2010;39:610–615.

    This study set out to test a new highly sensitive and specific pancreastatin assay against the known chromogranin A (CgA) assay currently in use in the United States. The tests showed up to a 100-fold increase in sensitivity and specificity.

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    This randomized controlled trial set out to set the reference range for urine 5-hydroxyindoleacetic acid (5-HIAA) from 947 specimens. The results showed that there were frequent elevations of urine 5-HIAA, and an elevated test result should only be used to corroborate a suspected carcinoid in the face of other consistent findings. They also note that 5-HIAA does not usually rise until carcinoid tumors have metastasized to the liver.

15. (2) **Janson ET** et al. Carcinoid tumors: Analysis of prognostic factors and survival in 301 patients from a referral center. Ann Oncol 1997;36(6):607–614.

    Three hundred one consecutive carcinoid patients were evaluated over 15 years with respect to tumor distribution, hormone production, prognostic factors, and survival. They found that survival was significantly shorter with midgut carcinoids, patients with greater than five liver metastases, high levels of 5-HIAA, plasma chromogranin A, or neuropeptide K.

16. (3) **Givi B** et al. Operative resection of primary carcinoid neoplasms in patients with liver metastases yields significantly better survival. Surgery 2006;140:891–896.

    A retrospective review of 84 patients of which 60 had primary resection. Resection of the primary neoplasm was associated with improved progression-free survival in patients with abdominal carcinoid.

17. (2) **Que FG** et al. Hepatic Surgery for metastatic gastrointestinal neuroendocrine tumors. Cancer Control 2002;9:67–79.

This review (57 references) evaluates the role as well as the rationale for cytoreductive hepatic surgery in the management of metastatic gastrointestinal neuroendocrine malignancies.

18. (4) **Dunne MJ** et al. Sandostatin and gastroenteropancreatic endocrine tumors—Therapeutic characteristics. In: O'Dorisio TM, ed. Sandostatin in the treatment of gastroenteropancreatic endocrine tumors. Consensus Round Table, Scottsdale (Arizona), March 22, 1987. Berlin, Springer Verlag: Sandoz Medical Publications, 1989:93–113.

This chapter is an in-depth review (35 references) of the therapeutic characteristics of Sandostatin. The authors show that Sandostatin has a low side effect profile and is beneficial for decreasing the symptoms of carcinoid tumors, including diarrhea, flushing, and increased serum levels of 5-hydroxyindoleacetic acid. They did not find any significant tumor size response to drug administration. These results were then assembled and used by Elton and colleagues for FDA approval in early 1989.

19. (2) **Arnold R** et al. Gastroenteropancreatic endocrine tumors: Effect of sandostatin on tumour growth. Digestion 1993;54:72–75.

One hundred fifteen gastroenteropancreatic patients with malignant endocrine tumors were entered into this prospective trial to determine the efficacy of 200 μg of Sandostatin on tumor growth. The study was able to show an initially favorable effect for 54% at 3 months; however, the effect was short lived as only 38% showed response at 12 months. They also proved that the effect mirrored the suppression of serum and urine hormone levels.

20. (2) **Paganelli G** et al. Receptor-mediated radiotherapy with 90Y-DOTA-D-Phel-Tyr3-octreotide. Eur J Nucl Med 2001;28(4):426–434.

This study took 30 consecutive patients with somatostatin receptor–positive tumors and looked at dosage, safety profile, and therapeutic efficacy. The patients were divided into groups of five and given subsequently higher doses of radiotherapy in increments of 0.37 GBq. Total injectable dose for this study was deemed limited by the estimated toxic dose to the kidneys of 20 to 25 Gy. The authors noted a complete or partial response in 23%, stable disease in 64%, and progression in 13%. They also concluded that high doses (total 7.77 GBq) were of low risk for myelotoxicity, but cumulative dose toxicity to the kidneys was still a risk factor and should be monitored closely.

21. (2) **Imhof A** et al. Response, survival, and long term toxicity after therapy with the radiolabeled somatostatin analogue (^{90}Y-DOTA)-TOC in metastasized neuroendocrine cancers. J Clin Oncol 2011;29:2416–2423.

Thousand one hundred nine patients were enrolled in an open-label phase II clinical trial of response to (^{90}Y-DOTA)-TOC. Significant response was shown morphologically, clinically, and biochemically, as well as improved survival. There were, however, both renal and hematologic sequelae associated with therapy.

11

Paraneoplastic Endocrine Syndromes

Subhash Kukreja

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Cancer cells frequently produce peptides that are not normally synthesized by the tissue of origin. In addition, peptides that are normally produced in a paracrine or autocrine manner may be produced in larger quantities by the cancer cells and released into the circulation. Cancer cells frequently lack the machinery to process peptides into mature hormones, and therefore, only precursor or incomplete forms of the protein are released. These partial peptides or precursor forms of the hormones may either be biologically inactive or may have weak biologic activity. Therefore, clinical syndromes due to ectopic production of these hormones are seen less frequently than might be predicted, based on the immunoassay studies. Ectopic production of steroid hormones by cancer cells is rare. However, steroid hormones may be present in higher concentration because of increased production of enzymes by the tumor cells e.g., synthesis of 1α-hydroxylase by certain lymphomas allows increase in the synthesis of 1,25-dihydroxyvitamin D [1,25$(OH)_2$D]. Another example is an increased aromatase activity in hepatocellular carcinoma with conversion of androgens to estrogens, resulting in gynecomastia.

Paraneoplastic syndrome is defined as the tumor-related clinical manifestations that occur distant from the site of the tumor and are mediated by humoral factors. Hypercalcemia of malignancy (HM) and syndrome of inappropriate antidiuretic hormone (SIADH) are the more common clinical syndromes due to ectopic hormone production. SIADH is covered elsewhere in this volume. The other ectopic endocrine syndromes are described in this chapter. There are other nonendocrine paraneoplastic manifestations of cancer, which are not covered in this chapter (e.g., polycythemia, various neuropathies, cerebellar degeneration, etc.).

HYPERCALCEMIA OF MALIGNANCY

Definition

Under physiologic conditions, serum calcium is maintained within a narrow range. Serum calcium is bound to proteins that are composed predominantly of albumin so that under normal conditions, approximately 45% of the calcium is available in the physiologically active, ionized, or free form. In the presence of hypoalbuminemia,

serum total calcium values may be low, whereas ionized calcium values may be normal or even elevated. Conversely, in some cases of multiple myeloma, abnormal globulins may bind calcium so that serum total calcium is high and ionized calcium is normal [1,2]. Various correction formulas have been devised to correct serum total calcium for serum protein/albumin concentrations. These correction formulas are derived from regression analysis of serum calcium and albumin/total proteins. None of these formulas accurately predicts the state of ionized calcium [3,4]; therefore, ionized calcium should be measured to assess the calcium status accurately when protein abnormalities are present.

HM is defined as the presence of elevated serum calcium levels in a patient with cancer (either solid tumor or hematologic) in whom the hypercalcemia is caused by factors produced by the cancer. This implies that the hypercalcemia should be reversed by the removal of the tumor. In practice, however, complete removal or cure of the tumor can rarely be achieved because the disease is often advanced by the time the diagnosis of hypercalcemia is made. Other diseases associated with hypercalcemia (e.g., primary hyperparathyroidism, sarcoidosis, excessive vitamin D intake) can occur coincidentally in patients with malignancy and should be excluded. This is particularly important because the presence of hypercalcemia in a patient with cancer indicates an extremely poor prognosis. If it can be shown that the hypercalcemia in a cancer patient is not due to malignancy, this may indicate a better prognosis.

Etiology

If bone metastases are present in a hypercalcemic cancer patient, it is traditionally assumed that the bone metastases are responsible for the hypercalcemia. In an examination of serum calcium values in patients with bone metastases, however, Ralston et al. [5] demonstrated that contrary to expectations, an inverse correlation existed between serum calcium levels and the number of bone metastatic lesions in patients with various malignancies. Hypercalcemia is frequently observed without significant bone metastases in certain types of tumors (e.g., squamous cell cancers), whereas in other tumors (e.g., small cell carcinoma of the lung and prostate cancer), bone metastases are frequently observed in the absence of hypercalcemia.

Bone resorption is increased in most patients with HM. Various osteolytic factors secreted by cancer cells have been described. These osteolytic factors may increase bone resorption by both local and endocrine effects. The major osteolytic factor produced by solid tumors is parathyroid hormone–related protein (PTHrP) [6]. The peptide has structural homology to parathyroid hormone (PTH) in only 8 of the first 13 amino acids, and yet a remarkable similarity exists in the biologic actions of the two peptides. Elevated levels of serum PTHrP are observed in patients with hypercalcemia resulting from solid tumors, including breast cancer [6]. Breast cancer cells derived from the bone marrow lesions produce PTHrP with greater frequency than do those derived from other metastatic sites [7].

In the case of multiple myeloma, other hematologic malignancies, various other cytokines, such as tumor necrosis factors, RANK ligand, interleukins (IL)-1 and -6, hepatocyte growth factor, and macrophage inflammatory protein-1α result in locally increased osteolysis [8]. Locally increased PTHrP production has also been demonstrated in these cancers as a mediator of increased osteolysis. In addition, serum PTHrP levels have been shown to be elevated in about one-third of patients with multiple myeloma and other hematologic malignancies [9]; therefore, PTHrP may contribute to the pathogenesis of hypercalcemia in these cancers through both local and endocrine mechanisms. Myeloma cells also produce factors that inhibit bone formation (DKK1, IL-3, IL-7, soluble frizzle-related

protein [FRP]-2), and the bone lesions due to myeloma often lack a reactive osteoblastic component resulting in a negative nuclear bone scan despite the presence of bone metastases [10].

HM has been classified as either humoral hypercalcemia of malignancy (HHM) based on absent or minimal bone involvement and an elevation in nephrogenous urine cAMP levels (due to increase in PTH-like effects on the kidney) or local osteolytic hypercalcemia (LOH) seen in patients with hematologic malignancies and breast cancer with extensive bone involvement [11]. While this is a useful concept, there may be significant overlap between the mechanisms responsible for these two types of HM.

Another factor that plays a role in the pathogenesis of hypercalcemia in Hodgkin and non-Hodgkin lymphomas is increased serum $1,25(OH)_2D$ production [12]. In these tumors, the lymphomatous tissue is able to convert 25-(OH)D into the active metabolite, $1,25(OH)_2D$. Serum $1,25(OH)_2D$ levels are elevated in these patients (unlike in hypercalcemia of solid tumors and multiple myeloma, where these levels are suppressed).

Therefore, PTHrP is the main factor responsible for the hypercalcemia in most solid tumors and in some hematologic malignancies. The local effects of PTHrP result in increased bone resorption, whereas the endocrine effects result in increased phosphaturia and relative decrease in urine calcium excretion. Serum PTHrP may be normal in some patients (up to 20% of patients) with HM due to solid tumors without bone metastases [13]. It is not known whether this represents the inability of the current assays to detect the type of PTHrP molecules that are present in these patients; alternatively, hypercalcemia in these patients may be caused by other unknown osteolytic factors. Increased 1α-hydroxylase activity resulting in increased serum $1,25(OH)_2D$ is the responsible factor in many cases of Hodgkin and non-Hodgkin lymphomas, whereas various cytokines may be responsible for the hypercalcemia in multiple myeloma and other hematologic malignancies. In patients with breast cancer, the hypercalcemia usually occurs at a time when there is extensive tumor bony involvement. However, serum PTHrP levels are elevated in many of these patients, suggesting an important role of this peptide in the development of hypercalcemia both in patients with or without bone metastases.

Epidemiology

Hypercalcemia has been reported to affect about 10% to 40% of all patients with cancer at some time during the course of the disease. However, this may reflect a selection bias, especially if the studies are done in hospitalized patients. Hypercalcemia occurs in late stages of cancer, and such patients are more likely to be hospitalized. At the time of initial presentation, the incidence of hypercalcemia in cancer patients is about 1% [14]. Non–small cell lung cancer, renal cancer, lymphoma, multiple myeloma, and breast cancer are the malignancies most commonly associated with hypercalcemia. The highest incidence of hypercalcemia on a percentage basis is observed in renal cell carcinoma [14]. Carcinoma of the prostate and colon and small cell carcinoma of the lung are rarely associated with hypercalcemia, despite a high prevalence of bone metastases in these cancers.

Pathophysiology

PTH-related protein, despite its limited homology to PTH, appears to act through the same receptor as PTH (PTH/PTHrP type I receptor). The clinical features of HM due to solid tumors are similar to those of hyperparathyroidism in many respects (e.g., hypercalcemia, hypophosphatemia, relative hypocalciuria, and increased bone resorption). In other aspects, manifestations of hypercalcemia malignancy due to PTHrP overproduction are different from those of primary

hyperparathyroidism, and these include relatively lower serum $1,25(OH)_2D$ and decreased bone formation observed in HM [15]. The decreased bone formation observed in HM may be related to the secretion of other cytokines (e.g., IL-1 and IL-6), although the mechanisms remain largely unexplained. In the case of Hodgkin and non-Hodgkin lymphomas, the elevated serum $1,25(OH)_2D$ levels enhance gastrointestinal (GI) calcium absorption, and serum PTH is suppressed with increased serum phosphate and urine calcium excretion.

Diagnosis

Primary hyperparathyroidism is the most common cause of hypercalcemia in the general population. In most instances, the hypercalcemia has been present for a long time and is mild to moderate. In HM, which is the second most common cause of hypercalcemia, the hypercalcemia is usually more severe and occurs over a relatively short time. This hypercalcemia manifests late in the course of the malignancy, and the tumor is generally advanced by the time diagnosis of hypercalcemia is confirmed. A complete history and physical examination and simple laboratory and radiologic studies would generally reveal the source of malignancy (i.e., lung cancer, head and neck cancer, carcinoma of the esophagus, breast cancer, multiple myeloma, lymphomas). Retroperitoneal tumors (e.g., renal cell cancer and some lymphomas) may not be readily apparent on initial evaluation, but even in these instances, clinical signs and simple imaging studies often reveal cancer. The laboratory test with the highest yield in the differential diagnosis of hypercalcemia is measurement of serum PTH. Serum PTH level is elevated or in the high-normal range in all patients with primary hyperparathyroidism. Conversely, serum PTH levels are suppressed in almost all cases of HM, with the rare exception of a few reported cases of the production of native PTH by cancer [16]. In the presence of a tumor type that is commonly associated with HM, the presence of suppressed PTH level confirms the etiology of hypercalcemia. If serum PTH levels are elevated, then the patient, in all likelihood, has concomitant hyperparathyroidism. If hypercalcemia is observed in association with a tumor type not commonly associated with hypercalcemia (e.g., small cell cancer of the lung, prostate cancer, colon cancer) and serum PTH levels are suppressed, another cause of the hypercalcemia should be sought. Serum PTHrP levels are increased in 80% to 100% of patients with hypercalcemia due to solid tumors, and this assay may be used in patients in whom the cause of hypercalcemia is not readily apparent. Serum $1,25(OH)_2D$ measurements is of value in the diagnosis of hypercalcemia in granulomatous disease and Hodgkin and non-Hodgkin lymphomas, in which these levels are usually elevated. Serum and urine protein electrophoresis is helpful for the diagnosis of multiple myeloma. In the presence of normal renal function, serum phosphate values are low or in the low-normal range in HM, similar to that seen in the primary hyperparathyroidism. Other tests (e.g., 24-hour urine calcium, urinary cyclic adenosine monophosphate [cAMP] measurements) are of limited value in the differential diagnosis.

Treatment

Patients with hypercalcemia are often volume depleted because of nausea, vomiting, and polyuria, which is a result of a decrease in urine-concentrating ability from a direct effect of hypercalcemia on the renal tubules. Infusion of 3 to 4 l/d of normal saline reduces the serum calcium concentration by 1.0 to 1.5 mg/dl. Increased bone resorption is the major mechanism by which the tumors produce hypercalcemia; agents that inhibit osteoclast activity are highly effective in management of these patients. The agents in this class are plicamycin, calcitonin, gallium nitrate, and bisphosphonates [17]. Bisphosphonates are potent antiresorptive agents that have become the drug of choice for treatment of

hypercalcemia. The first bisphosphonate to be used for this purpose was etidronate, but its use has been replaced by the second- and third-generation bisphosphonates (e.g., pamidronate, alendronate, and zoledronate). Intravenous pamidronate and zoledronate are now approved for treatment of HM. Pamidronate, 30 to 90 mg given over a 2- to 4-hour infusion, is as effective as the dose given over 24 hours. A flu-like syndrome is seen in up to 20% of patients, but this adverse effect is transient. Hypocalcaemia may occasionally occur in a small percentage of patients but is usually asymptomatic [18,19]. Zoledronate appears to be a more potent bisphosphonate than pamidronate [20]. More-rapid administration of zoledronate (i.e., over a 5-minute period) is associated with the risk of development of renal failure and therefore is not recommended. Other bisphosphonates, such as ibandronate and clodronate, are also effective. These latter compounds are not approved for use in the United States but are widely used in other countries [19]. The initial effects of bisphosphonates on reduction in serum calcium are observed within 12 to 24 hours, with peak effect being observed in 4 to 7 days. The effect generally lasts for 1 to 3 weeks, depending on the extent of PTHrP production by the tumor.

Hypercalcemic patients with Hodgkin and non-Hodgkin lymphomas, by a mechanism associated with increased $1,25(OH)_2D$ production, respond well to glucocorticoid therapy, for example, prednisone 20 to 40 mg/d. Patients with hypercalcemia resulting from multiple myeloma respond well to bisphosphonates and glucocorticoids.

Prognosis

The prognosis is poor for cancer patients by the time hypercalcemia becomes apparent, with a median survival of only 30 to 70 days [21,22]. In breast cancer with mild hypercalcemia (i.e., ionized serum calcium, 1.36–1.48 mmol/l), the prognosis is better, with a median survival of 17.7 months. Treatment of hypercalcemia is mainly palliative, and a decrease in serum calcium levels in these patients significantly improves symptoms and quality of life without affecting survival [21,22].

Antiresorptive Agents (Bisphosphonates and Denosumab) for Treatment of Bone Metastases

Laboratory evidence suggests that after the initial seeding and attachment of tumor cells to the bone marrow, increased osteolysis plays a significant role in the establishment and growth of tumor into the bone. In animal models, administration of agents that inhibit bone resorption results in reduction in the incidence and severity of bone metastases [23]. Therefore, a strong rationale exists for antiresorptive therapy to be helpful in the prevention and treatment of bone metastases. Newer bisphosphonates, such as zoledronate, may offer additional beneficial effects in reducing skeletal tumor growth by inhibition of angiogenesis through reduction of vascular endothelial growth factor (VEGF) levels [24]. A recent review of the available literature concluded that bisphosphonates such as pamidronate, zoledronate, ibandronate, and clodronate are effective in reducing the incidence of skeletal events, such as pathologic fracture, spinal cord compression, and hypercalcemia, without a proven benefit on prolonging survival [25–27]. Similarly, in patients with multiple myeloma and skeletal involvement, there is strong evidence that adding bisphosphonates to standard chemotherapy results in a reduction of future skeletal complications of pathologic fractures, skeletal-related events, and pain without offering a survival benefit [28].

Recent studies have shown the critical role of the RANK ligand in the osteoclast recruitment and development. In animal studies, inhibition of RANK ligand by osteoprotegerin results in potent inhibition of bone resorption and reversal

of hypercalcemia in two animal models of HHM [29]. A humanized antibody to RANK ligand, denosumab, has been developed and tested for prevention of skeletal events in malignancy. In recent large phase 3 trials, denosumab (120 mg SC every 4 weeks) when compared to zoledronate (4 mg IV every 4 weeks) showed greater suppression of bone turnover. In addition, denosumab was superior to zoledronate in reducing the rate of skeletal events (fracture, need for radiation treatment to bone, spinal cord compression) in patients with bone metastases due to breast cancer, prostate cancer, other solid tumors [30–32]. There were no differences in mortality rates. Denosumab is now approved for prevention of skeletal-related events (SREs) in patients with bone metastases from solid tumors. In patients with multiple myeloma with skeletal involvement, denosumab was as effective as zoledronate in preventing skeletal complications. However, in the ad hoc analysis, the mortality was slightly higher in the denosumab treatment group as compared to that in the zoledronate-treated group; the total number of patients in the multiple myeloma group were small [32]. Denosumab is not approved for prevention of bone disease in the patients with multiple myeloma. The incidence of hypocalcemia was greater with denosumab, while that of renal adverse events (AEs) was greater with the zoledronate treatment. There is a small but significant risk of osteonecrosis of the jaw, occurring to 1% to 2% of treated patient with either zoledronate or denosumab treatment.

HYPOCALCEMIA

Hypocalcemia is not a classic paraneoplastic syndrome in that there are no humoral factors that are released into the circulation, but excessive bone accretion due to local release of osteoblast-stimulating factors from the tumors may result in sequestration of calcium into the skeleton and thus lower serum calcium levels. Based on total serum calcium measurement, hypocalcemia is frequent in patients with cancers related to the low serum albumin and/or renal failure. True hypocalcemia, based on serum ionized calcium measurement, is less frequent and may be seen as a consequence of hyperphosphatemia due to rapid tumor lysis, hypomagnesemia, nephrotoxicity of certain chemotherapy agents, or direct inhibition of bone resorption. Tumor lysis syndrome is a medical emergency that occurs in patients with certain cancers and is caused by the rapid and massive breakdown of tumor cells, either spontaneously or after the initiation of radiation or chemotherapy. The rapid release of intracellular contents causes hyperuricemia, hyperkalemia, hyperphosphatemia, and secondary hypocalcemia (due to precipitation of calcium phosphate salts in to the soft tissues), and acute renal failure may develop [33]. Hypocalcemia may occur as a side effect of treatment with antibone resorptive agents such as bisphosphonates and denosumab for prevention of bone metastases.

Several cases of true hypocalcemia have been reported in patients with extensive osteoblastic bone metastases, especially in prostate cancer [34]. The hypocalcemia can be quite severe, and correction may require large amounts of oral or intravenous calcium and large doses of active vitamin D metabolites. The presumed mechanism for the hypocalcemia is the production of osteoblast-stimulating factor(s) by the tumor, which cause massive accretion of calcium into the skeleton. The exact nature of these factors is unknown, although multiple factors including endothelin-1, bone morphogenetic protein, transforming growth factor-beta (TGF-β), various growth factors including insulin-like growth factors (IGFs), and others have been proposed [35].

TUMOR-INDUCED OSTEOMALACIA

Tumor-induced osteomalacia (TIO), also referred to as oncogenic osteomalacia, is an acquired disorder of isolated renal phosphate wasting, seen in adults and

children, and is associated with tumors that are most commonly mesenchymal in origin. The manifestations of TIO are similar to those of patients with autosomal dominant hypophosphatemic rickets (ADHR) and X-linked hypophosphatemic rickets (XLH). Studies of tumors from patients with TIO led to discovery of circulating factors, referred to as "phosphatonins," which act upon the renal proximal tubule to decrease phosphate reabsorption. The major phosphotonin that was identified in these tumors is fibroblast growth factor 23 (FGF23), although other proteins such as matrix extracellular phosphoglycoprotein, FRP, and FGF7 have been isolated and have phosphaturic effects, but their role in TIO and in phosphate regulation remains largely unclear. FGF23 is normally produced by osteocytes, osteoblasts, flattened bone lining cells, and osteoprogenitor cells. Under physiologic conditions, hypophosphatemia increases 1α-hydroxylase activity; however, elevated FGF23 results in an inhibition of this activity despite the hypophosphatemia, thus resulting in low or inappropriately normal levels of $1,25(OH)_2$ vitamin D [36].

A common denominator in patients with TIO, XLH, and ADHR is the presence of elevated circulating FGF23 concentrations. The elevated FGF23 levels in TIO are due to its overproduction by the tumor cells [37]. The cause of elevated FGF23 in patients with XLH is inactivating mutation in the "phosphate-regulating gene with homologies to endopeptidases on the X chromosome (PHEX)." Although it was originally thought that PHEX is involved in degradation of FGF23, subsequent studies suggest that PHEX is involved in downregulation and control of FGF23; however, the precise interplay between FGF23 and PHEX is not yet completely understood. In ADHR, there is mutation in the FGF23 gene such that the protein is resistant to cleavage and degradation thus resulting in elevated levels [36].

The mesenchymal tumors that are associated with TIO are characteristically slow-growing, polymorphous tumors, which contain an admixture of spindle cells, osteoclast-like giant cells, prominent blood vessels, cartilage-like matrix, and metaplastic bone. Due to the small size and often unusual locations of these tumors, detection is frequently challenging. Standard imaging techniques, such as x-ray, computed tomography (CT) scan, and magnetic resonance imaging (MRI), can be initially used to detect tumors. However, other methods, such as ultrasonography, as well as labeling approaches, such as whole-body octreotide, 99mTc sestamibi, 201Tl, or F-18 FDG PET imaging, may be needed in other cases before a tumor can be localized [36].

The clinical manifestations of TIO are muscle weakness and muscle and bone pains and osteomalacia on X-rays. Serum P level is low, serum $1,25(OH)_2$ vitamin D is inappropriately low, and serum bone alkaline phosphatase levels are elevated along with increased serum FGF23 levels. Due the overlap of clinical symptoms with genetic and environmental causes of hypophosphatemia, the diagnosis of TIO cannot be made with certainty unless a neoplasm is detected and removed, and the clinical manifestations disappear. A careful family history is important in suspected TIO cases to rule out XLH, ADHR, and other inherited disorders of phosphorus metabolism; genetic studies may be needed. It can often take years and multiple imaging studies before the offending tumor can be localized. In the absence of the ability to identify and/or remove the tumors, these patients can present difficult management problems, needing large doses of phosphate and calcitriol and careful balance between GI side effects and maintaining appropriate serum P, calcium, and PTH levels [36].

ECTOPIC ADRENOCORTICOTROPIC HORMONE SYNDROME

Ectopic adrenocorticotropic hormone (ACTH) secretion accounts for 10% to 20% of all cases of Cushing syndrome. The common tumors associated with syndrome

are small cell lung cancer, bronchial carcinoids, medullary thyroid cancer, islet cell tumors, pheochromocytoma, and thymus tumors, although nonendocrine tumors may also be associated with the syndrome. Over 50% of the tumors are in the lung or the neck region. The clinical presentation can be varied, depending on the severity and rapidity of onset. In patients with malignant disease, such as small cell carcinoma of the lung, the onset may be rapid, and the classical features of Cushing syndrome such as weight gain and round plethoric facies may be absent; instead, the patient may present with hyperpigmentation (due to excessive secretion of proopiomelanocortin), weight loss, severe muscle weakness and wasting, hypokalemia, and hyperglycemia. On the other hand, patients with Cushing syndrome associated with benign bronchial carcinoid tumors tend to present with classic features that are indistinguishable from pituitary or adrenal-dependent disease [38,39]. The initial diagnosis of Cushing syndrome is made by establishing that there is inappropriate oversecretion of cortisol (elevated urine free cortisol, salivary cortisol, lack of suppression with low-dose dexamethasone, etc.) [40]. Plasma ACTH levels are elevated in both pituitary-dependent disease and ectopic ACTH syndrome. Although high-dose dexamethasone suppression test is used to differentiate between pituitary-dependent (>50% suppression) and ectopic Cushing syndrome (lack of suppression), there is a significant overlap in the results so that this cannot be used as the final test to plan therapy. Pituitary imaging may show a microadenoma in pituitary-dependent disease, but the tumor may not be evident in all cases, and small incidental pituitary tumors are common in the general population. No single endocrine test is accurate enough to distinguish ectopic from pituitary sources of ACTH; although concordant results from two or more tests provide a greater degree of certainty in establishing the cause. However, there is a general consensus that the bilateral inferior petrosal sinus sampling (IPSS) under corticotrophin-releasing hormone (CRH) and/or desmopressin stimulation is the gold standard to confirm pituitary ACTH hypersecretion [41,42]. Once it is established that the source of excessive ACTH production is not the pituitary gland, high-resolution cross-sectional imaging of various regions should be used to localize the source of ectopic ACTH production. Selective vein catheterization and radionuclide imaging may be helpful in selected cases. There are rare cases of ectopic CRH production resulting in Cushing syndrome, which can offer a diagnostic challenge [43].

The ideal treatment for ectopic ACTH syndrome is the removal of the tumor if one can be identified; however, tumor may never be identified in up to 20% of cases. In addition, complete removal of the primary tumor may not be possible, and the excessive cortisol secretion may continue after surgery. Bilateral adrenalectomy may be the only option to control hypercortisolemia in certain cases. Medical therapy with metyrapone and ketoconazole or cytolytic chemotherapy may be needed to control excessive cortisol secretion either prior to surgery or in cases where complete removal of the tumor and/or adrelectectomy is not feasible. Somatostatin and dopamine agonists have been used with good results in some patients, as some ACTH-producing tumors can express these receptors, but their role remains that of an adjuvant treatment [38,39].

Patients with ectopic ACTH associated with small cell lung cancer have the worst prognosis, with a median survival of 6 to 8 months. Patients with bronchial carcinoids have the best prognosis, while thymic tumors and pheochromocytomas carried an intermediate prognosis. Islet cell tumors and medullary carcinoma of the thyroid are frequently metastatic at the time of diagnosis, thus affecting prognosis and survival [38,39].

NON–ISLET CELL TUMOR–INDUCED HYPOGLYCEMIA

Hypoglycemia due to overproduction of insulin is seen in insulinomas. However, hypoglycemia can also occur due to secretion of IGF activity by certain tumors, and the syndrome is referred to as non–islet cell tumor–induced hypoglycemia (NICTH). The tumors associated with this syndrome are generally large mesenchymal or epithelial in origin (e.g., mesotheliomas, hepatocellular carcinoma, among others). Diagnosis of NICTH should be considered in these patients if they have hypoglycemic episodes or become unconsciousness. The hypoglycemic episodes may precede the diagnosis of the tumor [44]. The factor responsible for the hypoglycemia is the aberrant production of pro-IGF-II ("big" IGF-II), resulting in a persistent insulin-like activity; however, serum IGF-II levels may be normal in many patients with IGF-II-producing NICTH [45]. This indicates that a high-molecular-weight form, rather than the mature form, of IGF-II plays a role in the development of hypoglycemia. Under normal conditions, IGF-II binds to the IGF-binding protein-3 (IGFBP3) and an acid-labile subunit, forming a ternary complex of molecular weight of 150 kDa. However, the high-molecular-weight form of IGF-II does not bind to the acid-labile subunit but to the IGFBP to form a 40 to 50 kDa binary complex. This binary complex can pass through the capillary membranes and cause hypoglycemia via direct interaction with IGF and insulin receptors. Therefore, high-molecular-weight form of IGF-II has a greater bioavailability than mature IGF-II. Plasma GH and IGF-I levels are often suppressed. The diagnosis of NICTH is made on the basis of increased serum IGF-II/IGF-I ratio and/or elevated levels of the high-molecular-weight form of IGF-II [44,45]. Removal or ablation of tumor by chemotherapy or other means will cure the NICTH; however, often, this is not feasible. In these cases, large amounts of intravenous and oral glucose are needed to correct the hypoglycemia acutely. For longer term, glucocorticoids in moderate to high doses are the mainstay of therapy. Addition of growth hormone (GH) to glucocorticoids may be also helpful in certain cases to control symptoms [46,47].

ACROMEGALY

Acromegaly can result from the ectopic production of either GH or growth hormone–releasing hormone (GHRH), although both are rare [48]. Between the two, ectopic GHRH rather than GH is the more common cause. Immunoreactive GHRH can be secreted by multiple tumors including carcinoid tumors, pancreatic cell tumors, small cell lung cancers, endometrial tumors, adrenal adenomas, and pheochromocytomas; however, clinical acromegaly is uncommon in these patients. Regardless of the cause, GH and IGF-1 levels are invariably elevated, and GH levels fail to suppress after an oral glucose load in all forms of acromegaly. Dynamic pituitary tests are not helpful in distinguishing acromegalic patients with pituitary tumors from those harboring extrapituitary tumors. Plasma GHRH levels are usually elevated in patients with peripheral GHRH-secreting tumors and are normal or low in patients with pituitary acromegaly [49]. Ectopic GH secretion is rare and has been reported in association with carcinoid tumors [50]. Various imaging modalities, including spiral CT of thorax, octreotide scan, etc., should be performed to localize the cause of GHRH or GH production in a patient with acromegaly where the pituitary imaging does not reveal a tumor.

Surgical resection of the tumor secreting ectopic GHRH or GH production is the first treatment approach. Somatostatin analogs provide an effective option for medical management of carcinoid tumors, especially those with recurrent disease. Long-acting somatostatin analogs may be able to control not only the ectopic hormonal secretion syndrome but also, in some instances, tumor growth [49].

HYPERTHYROIDISM

Human chorionic gonadotropin (hCG) is a weak TSH agonist and causes increased cyclic cAMP, iodide transport, and cell growth in thyroid cell cultures. Trophoblastic tumors, hydatidiform mole, and choriocarcinoma often cause hyperthyroidism because they secrete very large amounts of hCG. When the serum hCG exceeds about 200 IU/ml, hyperthyroidism is likely to be found. There is a correlation between the biochemical severity of hyperthyroidism and the serum hCG in these patients. Removal of the mole or effective chemotherapy of the choriocarcinoma cures the hyperthyroidism [51,52].

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1. (3) **Pearce CJ** et al. Hypercalcaemia due to calcium binding by a polymeric IgA kappa-paraprotein. Ann Clin Biochem 1991;28:229–234.

   A patient with multiple myeloma and elevation in total serum calcium and normal ionized calcium is described. In vitro studies demonstrated that there was abnormal binding of calcium to the paraprotein IgAκ, thus explaining the false finding of hypercalcemia.

2. (2) **Smith BJ** et al. Frequency of calcium binding by monoclonal immunoglobulins in multiple myeloma. Ann Clin Lab Sci 1984;14:261–264.

   To examine the frequency with which abnormal binding to paraprotein may result in elevated serum total with normal ionized calcium values, the authors studied 34 patients with multiple myeloma. Both total and ionized calcium were elevated in three patients. In this series, no abnormal binding between the paraproteins and calcium was observed. This suggests that falsely elevated serum calcium levels are not common in patients with multiple myeloma.

3. (2) **Ladenson JH** et al. Failure of total calcium corrected for protein, albumin, and pH to correctly assess free calcium status. J Clin Endocrinol Metab 1978;46:986–993.

   The authors used various published formulas to correct observed calcium for serum protein and albumin abnormalities in 2,454 samples sent for calcium analysis and correlated these values to the measured ionized calcium levels. None of the formulas produced substantially better agreement than that observed between the uncorrected calcium and ionized calcium. The studies concluded that correction of measured serum calcium does not seem to adequately predict calcium status as measured by free calcium.

4. (3) **Shemerdiak WP** et al. Evaluation of routine ionized calcium determination in cancer patients. Clin Chem 1981;27:1621–1622.

   In this study, serum total and ionized calcium levels were determined in 59 controls and 95 cancer patients. Various correction formulas were used to determine whether these would predict the calcium status better than that predicted from measurement of total calcium alone. Of the 95 cancer patients, 12 were judged to be hypercalcemic by both total and ionized calcium measurement. An additional 11 patients were found to have elevated ionized with normal total calcium values; the serum calcium elevation in these patients, however, was mild. Application of various correction formulas did not aid significantly in identifying these patients. The study concluded that for most cancer patients, total calcium measurement is adequate. In the presence of protein abnormalities, correction formulas do not aid in correct classification of the calcium status. In these patients, ionized calcium should be determined to assess calcium status accurately.

5. (2) **Ralston S** et al. Hypercalcaemia and metastatic bone disease: Is there a causal link? Lancet 1982;2:903–905.

   Bone scans in 725 unselected cancer patients at the Glasgow Royal Infirmary were reviewed. Further analysis was performed in 160 patients with definite metastatic bone disease and 35 hypercalcemic patients without bone metastasis. Bronchogenic and breast cancer were the two most common diagnoses (48% and 31%, respectively). Of the total of 87 hypercalcemic patients, 40% had no evidence of bone metastases, and only 32.5% of the patients with bone metastases had hypercalcemia. The adjusted total serum calcium levels were significantly lower in patients with extensive metastatic disease (>6 lesions on bone scan) compared with those with milder disease (<6 lesions on bone scan). The authors concluded that a causal link does not appear to exist between bone metastasis and hypercalcemia.

6. (4) **Rankin W** et al. Parathyroid hormone-related protein and hypercalcemia. Cancer 1997;80(suppl):1564–1571.

   An excellent review of the discovery and physiology of PTH-related protein and of the evidence linking it to the pathogenesis of HM including that observed in breast cancer.

7. (4) **Martin TJ** et al. Mechanisms in the skeletal complications of breast cancer. Endocr Relat Cancer 2000;7:271–284.

About 70% of patients with advanced breast cancer will have metastatic bone disease, and about 30% of patients will experience hypercalcemia. The review describes that various osteolytic factors such as PTHrP may be involved in the pathogenesis of both of these manifestations of cancer.

8. (4) **Callander NS** et al. Myeloma bone disease. Semin Hematol 2001;38:276–285.

Bone destruction occurs in 70% to 80% of patients with multiple myeloma. This is an excellent review of the various osteoclast-activating factors implicated in the pathogenesis of myeloma bone disease. These include tumor necrosis factors, RANK ligand, IL-1 and IL-6, hepatocyte growth factor, and macrophage inflammatory protein-1a. Bone cytokines (e.g., IL-6) are released as a result of the osteolysis and may in turn play a role in the stimulation of myeloma cell growth. This provides the rationale for the use of antiresorptive therapy in the management of multiple myeloma.

9. (2) **Firkin F** et al. Parathyroid hormone-related protein in hypercalcaemia associated with haematological malignancy. Br J Haematol 1996;94:486–492.

In this prospective study of patients admitted to a clinical hematology unit, hypercalcemia was detected in 18 of 165 patients. Of the 17 patients who were investigated further, hypercalcemia was ascribed to primary hyperparathyroidism in three patients. The other cases of hypercalcemia occurred as follows: nine with multiple myeloma, five with B-cell non-Hodgkin lymphoma, and one with myeloid hyperplasia. PTHrP levels were elevated and correlated with serum calcium level elevation in three of nine myeloma cases and two of four lymphoma patients. Therefore, PTHrP appears to be involved in the pathogenesis of hypercalcemia in hematologic malignancies.

10. (4) **Roodman GD**. Pathogenesis of myeloma bone disease. Leukemia 2009;23:435–441.

In this review, there is detailed description of the mechanism and the factors that are responsible in the development of bone disease seen in multiple myeloma. It is shown that in addition to the increased bone formation, there is significant component of decreased bone formation in these patients, and these factors (DKK1, IL-3, IL-7, soluble FRP-2) are described.

11. (2) **Stewart AF** et al. Biochemical evaluation of patients with cancer-associated hypercalcemia: Evidence for humoral and nonhumoral groups. N Engl J Med 1980;303:1377–1383.

In this prospective study of 50 consecutive hypercalcemic cancer patients seen at a university hospital, urine cAMP, serum calcium, PTH, and $1,25(OH)_2D$ levels were determined. Urine nephrogenous cAMP levels (a marker of PTH action on kidney) were elevated in 41 patients with HM and in patients with primary hyperparathyroidism. Serum PTH levels were elevated in patients with primary hyperparathyroidism and low in cancer patients. The studies provided strong evidence that the humoral factor or factors responsible for hypercalcemia have strong similarity of biologic action to that of PTH and yet are different immunologically. This and other similar studies laid the foundation for later discovery of the PTHrP. The study also described that serum $1,25(OH)_2D$ levels are lower in HM, as compared with those seen in primary hyperparathyroidism.

12. (3) **Seymour JF** et al. Calcitriol production in hypercalcemic and normocalcemic patients with non-Hodgkin lymphoma. Ann Intern Med 1994;121:633–640.

In this prospective study performed at a referral medical center, serum $1,25(OH)_2D$ levels were elevated in 12 of the 22 hypercalcemic patients using a reference range developed by using hypercalcemic myeloma patients as the control population. If the reference range from normocalcemic subjects were used, only half the patients would be classified as having elevated $1,25(OH)_2D$ levels.

13. (3) **Burtis WJ** et al. Immunochemical characterization of circulating parathyroid hormone-related protein in patients with humoral hypercalcemia of cancer. N Engl J Med 1990;322:1106–1112.

In this study, serum PTHrP levels were measured in patients with HM. Plasma PTHrP levels were elevated in 25 of 30 patients with HHM and none of the 8 patients with LOH. Therefore, measurement of plasma PTHrP levels may be useful in differential diagnosis of hypercalcemia.

14. (2) **Vassilopoulou-Sellin R** et al. Incidence of hypercalcemia in patients with malignancy referred to a comprehensive cancer center. Cancer 1993;71:1309–1312.

In this retrospective analysis of laboratory data from 7,667 patients registered at a referral cancer center, the incidence of hypercalcemia within the first 2 months of the registration was determined. Severe hypercalcemia, defined as serum calcium level above 12 mg/dl, was present in 40 (0.52%), and moderate hypercalcemia, defined as serum calcium levels of 10.8 to 12 mg/dl, was present in an additional 48 patients (0.63%), with a total incidence of 1.05%. Non–small cell lung cancer, renal cancer, lymphoma, multiple myeloma, and breast cancer

were the malignancies most commonly associated with hypercalcemia. The highest incidence of hypercalcemia on a percentage basis was observed in renal cell carcinoma. Carcinoma of the prostate and colon and small cell carcinoma of the lung are rarely associated with hypercalcemia, despite a high prevalence of bone metastases in these cancers.

15. (4) **Stewart AF**. Clinical practice: Hypercalcemia associated with cancer. N Engl J Med 2005;352:373–379.

    This review offers practical updated information on the diagnosis and treatment for patients with hypercalcemia associated with malignancy.

16. (2) **Nussbaum SR** et al. Highly sensitive two-site immunoradiometric assay of parathyrin, and its clinical utility in evaluating patients with hypercalcemia. Clin Chem 1987;33:1364–1367.

    A highly sensitive and specific two-site immunoradiometric for serum PTH is described. There was a complete separation of serum PTH values between 37 patients with surgically proven primary hyperparathyroidism and 23 patients with hypercalcemia of cancer. In HM, PTH levels were at or below the lower limits of normal. Subsequent studies performed in several hundreds of patients with both syndromes have confirmed these findings.

17 (2) **Ralston SH** et al. Comparison of aminohydroxypropylidene diphosphonate, mithramycin, and corticosteroids/calcitonin in treatment of cancer-associated hypercalcaemia. Lancet 1985;2:907–910.

    Thirty-nine patients with hypercalcemia due to cancer were randomly assigned to receive aminohydroxypropylidene diphosphonate (pamidronate, 15 mg daily in saline until serum calcium normalized), mithramycin (plicamycin, 25 mg/kg and repeated 48 hours later if serum calcium was still elevated), or calcitonin plus corticosteroids (salmon calcitonin, 400 MRC units every 8 hours, and prednisolone, 40 mg/d). Calcitonin/corticosteroids had the fastest onset of action (<24 hours), but the effects were short-lived, with most patients remaining hypercalcemic during days 6 to 9 after start of treatment. Plicamycin's effect was seen within 48 hours, and it lasted for 6 to 9 days. Pamidronate's effect was at 72 hours, but it lasted for longer than 9 days.

18. (2) **Nussbaum SR** et al. Single-dose intravenous therapy with pamidronate for the treatment of hypercalcemia of malignancy: Comparison of 30-, 60-, and 90-mg dosages. Am J Med 1993;95:297–304.

    In this double-blind, randomized, multicenter clinical trial, 50 cancer patients with corrected serum calcium above 12 mg/dl were treated with pamidronate, 30, 60, or 90 mg given as a 24-hour infusion. Serum calcium corrected in 40%, 61%, and 100% of patients receiving the 30-, 60-, and 90-mg doses, respectively. The median duration of action was 4, 5, and 6 days in the three groups, respectively.

19. (4) **Body JJ**. Current and future directions in medical therapy: Hypercalcemia. Cancer 2000;88(suppl):3054–3058.

    This is a review of the current management of hypercalcemia of cancer, including a comparison of the newer second- and third-generation bisphosphonates (e.g., clodronate, pamidronate, ibandronate, zoledronate). After initial hydration, bisphosphonates are the most effective treatments available. Control of the hypercalcemia can be obtained in more than 90% of cases with the use of bisphosphonates.

20. (1) **Major P** et al. Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: A pooled analysis of two randomized, controlled clinical trials. J Clin Oncol 2001;19:558–567.

    In this pooled analysis of two parallel multicenter randomized trials, 275 patients were evaluated for efficacy of 4- or 8-mg zoledronate given as a 5-minute infusion or 90-mg pamidronate given as a 2-hour infusion. The complete response rates by day 10 were 88.4%, 86.7%, and 69.7% for 4-mg zoledronate, 8-mg zoledronate, and 90-mg pamidronate, respectively. The median duration of complete response was 32, 43, and 18 days, respectively. The study indicates that zoledronate, 4 or 8 mg, is superior to pamidronate in the management of hypercalcemia of cancer.

21. (3) **Ralston SH** et al. Cancer-associated hypercalcemia morbidity and mortality: Clinical experience in 126 treated patients. Ann Intern Med 1990;112:499–504.

    This was a retrospective analysis of 126 consecutive patients with cancer-associated hypercalcemia in a teaching hospital in the United Kingdom. The study examined the effects of medical calcium-lowering treatment on symptom relief and survival in 126 patients with various cancers (squamous cell lung cancer was the most common with 43 cases and breast cancer the second most common with 22 cases). The survival rate depended on whether specific anticancer therapy was possible (26 patients) in whom the median survival was 135 days compared with a survival of 30 days for those who did not receive anticancer treatment. There were significant palliative benefits from antihypercalcemic therapy. The symptoms of polyuria, constipation, anorexia, nausea/vomiting, and lethargy improved significantly after serum calcium levels

were controlled. In many cases, symptoms improved enough to allow patients to be discharged from the hospital.

22. (2) **Kristensen B** et al. Survival in breast cancer patients after the first episode of hypercalcaemia. J Intern Med 1998;244:189–198.

The study was conducted in a cancer center in Denmark. A consecutive cohort of 212 hypercalcemic breast cancer patients was observed during follow-up to determine survival. Of these, 193 patients had bone metastases and were further analyzed based on serum calcium levels. The patients continued to receive other treatments for cancer. The median survival for the overall group was 6.7 months. The median survival rates in patients with mild hypercalcemia (ionized calcium, 1.36–1.48 mmol/l; $n = 102$), moderate hypercalcemia (1.49–1.60 mmol/l; $n = 41$), and severe hypercalcemia) > 1.6 mmol/l; $n = 50$) were 17.7, 2.8, and 1.4 months, respectively. A second group of 51 hypercalcemic patients who received bisphosphonates was also studied. Survival in this group was not significantly different than in those who did not receive these agents. Survival in breast cancer is decreased significantly in patients with moderate to severe hypercalcemia. It was also shown that bisphosphonate treatment does not prolong survival.

23. (4) **Guise TA** et al. Understanding and optimizing bone health in breast cancer. Curr Med Res Opin 2010;26(suppl 3):3–20.

This review describes the significant role of increased bone resorption in the development of bone metastases and associated skeletal events such as pain, pathologic fractures, spinal compression, and hypercalcemia, which affect quality of life in patients with breast cancer. In addition, chemotherapy and aromatase inhibitors add to the bone loss. The review describes the preclinical and clinical studies, which support a role of inhibitors of bone resorption in preventing the skeletal events due to cancer and its treatment in breast cancer. In addition, antitumor activity of current bone-targeted agents in patients with breast cancer is explored.

24. (2) **Vincenzi B** et al. Zoledronic acid-related angiogenesis modifications and survival in advanced breast cancer patients. J Interferon Cytokine Res 2005;25:144–151.

Forty-two consecutive breast cancer patients with scintigraphic and radiographic evidence of bone metastases were treated with a single infusion of 4 mg zoledronic acid (ZA) before anticancer chemotherapy. There was a significant reduction in circulating levels of VEGF after 21 days in 60% of patients. The analysis of survival showed that patients with a reduction in the circulating VEGF levels had a longer time to first skeletal-related event (SRE) ($p = 0.0002$), time to bone progression disease ($p = 0.0024$), and time to performance status worsening ($p = 0.0352$) than those without the VEGF reduction.

25. (1) **Hillner BE** et al. American Society of Clinical Oncology guideline on the role of bisphosphonates in breast cancer: American Society of Clinical Oncology Bisphosphonates Expert Panel. J Clin Oncol 2000;18:1378–1391.

A review of the current literature on the use of bisphosphonates shows no impact on overall survival (OS). The review indicates there are benefits, such as reductions in skeletal complications (i.e., pathologic fractures), surgery for fracture or impending fracture, radiation, spinal cord compression, and hypercalcemia. Intravenous pamidronate, 90 mg delivered over 1 to 2 hours every 3 to 4 weeks, is recommended in patients with metastatic breast cancer who have imaging-confirmed evidence of lytic destruction of bone and who are concurrently receiving systemic therapy with hormonal therapy or chemotherapy. For women with abnormal bone scan results but with no bony destruction revealed by imaging studies and no localized pain, insufficient evidence exists to suggest use of bisphosphonates. Starting bisphosphonate therapy in patients without evidence of bony metastasis, even in the presence of other extraskeletal metastases, is not recommended.

26. (1) **Wong R** et al. Bisphosphonates for the relief of pain secondary to bone metastases. Cochrane Database Syst Rev 2002;2:CD002068.

This review included 30 randomized controlled studies (21 blinded, 4 open, and 5 actively controlled) with a total of 3,682 subjects. In the eight studies in which pain could be evaluated, pooled data showed benefits for the treatment group, with a number needed to treat of 11 at 4 weeks (95% CI, 6–36) and of 7 at 12 weeks (95% CI, 5–12). One study showed a small improvement in quality of life for the treatment group at 4 weeks. Bisphosphonates should be considered as a second-line therapy.

27. (1) **Pavlakis N** et al. Bisphosphonates for breast cancer. Cochrane Database Syst Rev 2005;3:CD003474.

Twenty-one randomized studies were included. All studies in advanced breast cancer included women with clinically evident bone metastases (osteolytic and/or mixed osteolytic/osteoblastic) by plain radiograph and/or radionucleotide bone scans. Overall, intravenous bisphosphonates reduced the risk of developing a skeletal event by 17% (95% CI, 0.78–0.89) compared with oral bisphosphonates, which reduce the risk of developing a skeletal event by 16% (95% CI,

0.76–0.93). Of the currently available bisphosphonates, 4-mg IV zoledronate reduces the risk of developing a skeletal event by 41% (RR, 0.59; 95% CI, 0.42–0.82), compared with 33% by 90-mg IV pamidronate (RR, 0.77; 95% CI, 0.69–0.87), 18% by 6-mg IV ibandronate (RR, 0.82; 95% CI, 0.67–1.00), 14% by 50-mg oral ibandronate (RR, 0.86; 95% CI, 0.73–1.02), and 16% by 1,600-mg oral clodronate (RR, 0.84; 95% CI, 0.72–0.98). Overall conclusion of the analysis revealed that in women with advanced breast cancer and clinically evident bone metastases, the use of bisphosphonates (oral or intravenous) in addition to hormone therapy or chemotherapy, when compared with placebo or no bisphosphonates, reduces the risk of developing a skeletal event and the skeletal event rate as well as increases the time to skeletal event. Some bisphosphonates may also reduce bone pain in women with advanced breast cancer and clinically evident bone metastases and may improve global quality of life. The optimal timing of initiation of bisphosphonate therapy and duration of treatment is uncertain. In women with early breast cancer, the effectiveness of bisphosphonates remains an open question for research.

28. (1) **Mhaskar R** et al. Bisphosphonates in multiple myeloma. Cochrane Database Syst Rev 2010;17:CD003188.

    This review includes 17 trials with 1,520 patients analyzed in bisphosphonates groups, and 1,490 analyzed in control groups. In comparison with placebo/no treatment, the pooled analysis demonstrated the beneficial effect of bisphosphonates on prevention of pathologic vertebral fractures (RR = 0.74; 95% CI, 0.62–0.89; $p = 0.001$), total SREs (RR = 0.80; 95% CI, 0.72–0.89; $p < 0.0001$), and on amelioration of pain (RR = 0.75; 95% CI, 0.60–0.95; $p = 0.01$). There was no significant effect of bisphosphonates on OS, progression-free survival, hypercalcemia, or on the reduction of nonvertebral fractures. It is estimated that between 8 and 20 multiple myeloma patients need to be treated to prevent one vertebral fracture and between 5 and 13 patients would need to be treated to reduce pain in one patient. No bisphosphonate appears to be superior to others.

29. (2) **Morony S** et al. The inhibition of RANKL causes greater suppression of bone resorption and hypercalcemia compared with bisphosphonates in two models of humoral hypercalcemia of malignancy. Endocrinology 2005;146:3235–3243.

    The authors used the RANKL inhibitor osteoprotegerin (OPG) to evaluate the role of osteoclast-mediated hypercalcemia in two murine models of HHM. In both models, OPG (0.2–5 mg/kg) caused rapid reversal of established hypercalcemia, and the speed and duration of hypercalcemia suppression were significantly greater with OPG (5 mg/kg) than with high-dose bisphosphonates (pamidronate or ZA, 5 mg/kg). OPG also caused greater reductions in osteoclast surface and biochemical markers of bone resorption compared with either bisphosphonate. Antiresorptive therapy with a RANKL inhibitor might be a rational approach to controlling HHM.

30. (1) **Stopeck AT** et al. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: A randomized, double-blind study. J Clin Oncol 28:5132–5139.

    In this study, the effects of subcutaneous denosumab 120 mg or intravenous ZA 4 mg every 4 weeks were compared in patients with breast cancer with metastases on the future occurrence of SRE (defined as pathologic fracture, radiation or surgery to bone, or spinal cord compression). Denosumab was superior to ZA in delaying time to first on-study SRE (hazard ratio, 0.82; 95% CI, 0.71–0.95; $p = 0.01$ superiority) and time to first and subsequent (multiple) on-study SREs (rate ratio, 0.77; 95% CI, 0.66–0.89; $p = 0.001$). Reduction in bone turnover markers was greater with denosumab. OS, disease progression, and rates of AEs and serious AEs were similar between groups. An excess of renal AEs and acute-phase reactions occurred with ZA; hypocalcemia occurred more frequently with denosumab. Osteonecrosis of the jaw occurred infrequently (2.0%, denosumab; 1.4%, ZA; $p = 0.39$).

31. (1) **Fizazi K** et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: A randomised, double-blind study. Lancet 2011;377:813–822.

    The study compared denosumab with ZA for prevention of SREs in men with bone metastases from castration-resistant prostate cancer. Median time to first on-study SRE was 20.7 months (95% CI, 18.8–24.9) with denosumab compared with 17.1 months (15.0–19.4) with ZA (hazard ratio, 0.82; 95% CI, 0.71–0.95; $p = 0.0002$ for noninferiority; $p = 0.008$ for superiority). The total numbers of skeletal events were also significantly reduced by denosumab as compared to those seen with ZA treatment. There were no significant differences in the mortality between the two groups.

32. (1) **Henry DH** et al. Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. J Clin Oncol 2011:29:1125–1132.

    The study compared the effects of denosumab with ZA for delaying or preventing SRE in patients with advanced cancer and bone metastases (excluding breast and prostate) or myeloma. Denosumab was noninferior to ZA in delaying time to first on-study SRE (hazard

ratio, 0.84; 95% CI, 0.71–0.98; $p = 0.0007$). Although directionally favorable, denosumab was not statistically superior to ZA in delaying time to first on-study SRE ($p = 0.03$ unadjusted; $p = 0.06$ adjusted for multiplicity) or time to first and subsequent (multiple) SRE (rate ratio, 0.90; 95% CI, 0.77–1.04; p = 0.14). Although, OS and disease progression were similar between groups as a whole, an ad hoc subgroup analysis showed a significant survival benefit in non–small cell lung cancer and a decreased survival in patients with multiple myeloma (the numbers of patients with multiple myeloma was small).

33. (4) **Abu-Alfa AK** et al. Tumor lysis syndrome and acute kidney injury: Evaluation, prevention, and management. Am J Kidney Dis 2010;55(suppl 3):S1–S13.

    The review describes the risk factors, pathogenesis, presentation, and prevention strategies for the tumor lysis syndrome seen in cancer patients. To prevent hypocalcemia, it is best to avoid hyperphosphatemia by using dietary phosphate restriction and administration of oral phosphate binders, forced diuresis with furosemide, dialysis, or hemofiltration. It is best to avoid IV calcium administration unless hypocalcemia is symptomatic because it might increase the risk of calcium phosphate precipitation and the potential for additional kidney injury.

34. (2) **Kukreja SC** et al. Hypocalcemia in patients with prostate cancer. Calcif Tissue Int 1988;43:340–345.

    This article describes a case of severe hypocalcemia in a patient with extensive osteoblastic metastases due to prostate cancer. Prevalence of hypocalcemia was examined in an additional 112 patients. The prevalence of true hypocalcemia based on ionized calcium measurement in patients with prostate cancer is low (<2%), even though total calcium levels decrease in up to 14%; most of these patients have bone metastasis.

35. (4) **Ibrahim T** et al. Pathogenesis of osteoblastic bone metastases from prostate cancer. Cancer 2010;116:1406–1418.

    The review describes the various factors that are produced by prostate cells and interact with the osteoblast cells. Many of these factors have effects on differentiation, proliferation, and migration of osteoblasts and may be involved in the pathogenesis of the osteoblastic metastases. These factors include endothelin 1, bone morphogenetic protein, IGF, FGF, platelet-derived growth factor, prostate-specific antigen, urokinase-type plasminogen activator, VEGF, TGF-β, and parathyroid hormone–related protein.

36. (4) **Farrow EG** et al. Tumor-induced Osteomalacia. Expert Rev Endocrinol Metab 2009;5:435–442.

    This is an excellent review of the clinical features, pathogenesis, differential diagnosis, and value of various diagnostic tools in the management of patients with TIO.

37. (2) **Shimada T** et al. Cloning and characterization of FGF23 as a causative factor of tumor-induced osteomalacia. Proc Natl Acad Sci U S A 2001;98:6500–6505.

    In this study, the authors identified that FGF23 is the hypophosphatemic factor synthesized and secreted by a tumor associated with oncogenic osteomalacia. FGF23 administration reproduced the clinical features of the disease in mice including low 1,25(OH)D levels. The increased production of FGF23 in oncogenic osteomalacia appears to be the link that explains phosphate wasting in this syndrome.

38. (4) **Isidori AM** et al. Ectopic ACTH syndrome. Arq Bras Endocrinol Metabol 2007;51:1217–1225.

    This is an excellent review of the topic describing clinical features, epidemiology, diagnostic, and treatment approaches to patients with ectopic Cushing syndrome.

39. (4) **Alexandraki KI** et al. The ectopic ACTH syndrome. Rev Endocr Metab Disord 2010;11:117–126.

    This is an updated review of ectopic Cushing syndrome.

40. (1) **Nieman LK** et al. The diagnosis of Cushing's syndrome: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2008;93(5):1526–1540.

    The paper describes the guidelines published by the Endocrine Society for the diagnosis of Cushing syndrome. An evidence-based approach is presented for the best available diagnostic strategies. The authors also describe the modification of these tests in special situations such as patients on various drugs, renal insufficiency, pregnancy, etc.

41 (3) **Ilias I** et al. Cushing's syndrome due to ectopic corticotropin secretion: Twenty years experience at the National Institutes of Health. J Clin Endocrinol Metab 2005;90:4955–4962.

    The authors report their experience in diagnosing and treating 90 patients with ectopic Cushing syndrome at a tertiary care clinical research center. Eighty-six percent to ninety-four percent of patients did not respond to CRH or dexamethasone suppression, whereas 66 of 67 had negative IPSS. To control hypercortisolism, 62 patients received medical treatment,

and 33 had bilateral adrenalectomy. Imaging localized tumors in 67 of 90 patients. Surgery confirmed an ACTH-secreting tumor in 59 of 66 patients and cured 65%. The authors concluded that a negative IPSS is the best test in identifying ectopic ACTH syndrome. Although only 47% achieved cure, survival is good, except in patients with small cell lung cancer, medullary thyroid cancer, and gastrinoma.

42. (3) **Kaltsas GA** et al. A critical analysis of the value of simultaneous inferior petrosal sinus sampling in Cushing's disease and the occult ectopic adrenocorticotropin syndrome. J Clin Endocrinol Metab 1999;84:487–492.

In this study, the frequency of occult ectopic Cushing syndrome was found to be 5.5% (six cases compared with 107 cases for Cushing disease). IPSS after CRH showed an inferior petrosal sinus/peripheral gradient less than 2 in all cases of ectopic ACTH syndrome. A bilateral inferior petrosal sinus/peripheral ratio that exceeded 2, obtained 5 minutes after CRH stimulation, had a sensitivity of 97% and a specificity of 100% in diagnosing Cushing disease.

43. (3) **Shahani** et al. Ectopic corticotropin-releasing hormone (CRH) syndrome from metastatic small cell carcinoma: A case report and review of the literature. Diagn Pathol 2010;5:56.

A patient with metastatic liver disease due to an endocrine tumor and Cushing syndrome is described, where pituitary imaging was normal and cortisol did not suppress with a high-dose dexamethasone, consistent with a diagnosis of ectopic ACTH syndrome. The tumor cells were negative for ACTH but positive for CRH by immunostaining, and plasma CRH levels were elevated.

44. (3) **Jan Willem B de Groot** et al. Non-islet cell tumour-induced hypoglycaemia: A review of the literature including two new cases. Endocr Relat Cancer 2007;14:979–993.

The report describes two new cases of NICTH and provides an excellent review of the pathogenesis and diagnostic and management strategies.

45. (2) **Hizuka N** et al. Serum insulin-like growth factor II in 44 patients with non-islet cell tumor hypoglycemia. Endocr J 1998;45(suppl):S61–S65.

Serum levels of pro-IGF-II ("big" IGF-II) were elevated in 31 of the 44 patients with non–islet cell tumor hypoglycemia. Elevated IGF-II levels were found in only 13 of the 31 patients. Serum IGF-I levels were low in all patients, including 11 patients who did not have elevated IGF-II levels. It is suggested that both a high IGF-II level and low IGF-I level play a role in the pathogenesis of the syndrome.

46. (3) **Drake WM** et al. Dose-related effects of growth hormone on IGF-I and IGF-binding protein-3 levels in non–islet cell tumour hypoglycaemia. Eur J Endocrinol 1998;139:532–536.

The authors treated two patients with non–islet cell tumor hypoglycemia by using recombinant GH. This treatment resulted in an increased serum IGF-I and IGFBP3 levels and an amelioration of hypoglycemia. The mechanism of the beneficial effect appears partly related to the increased IGFBP3 levels, with resultant decrease in free serum IGF-II levels. The IGFBP3 levels, however, did not completely normalize despite high-dose GH therapy, suggesting that other mechanism may be involved in explaining the beneficial effects of GH therapy in this syndrome.

47. (3) **Bourcigaux N** et al. Treatment of hypoglycemia using combined glucocorticoid and recombinant human growth hormone (HGH)in a patient with a metastatic non-islet cell tumor hypoglycemia. Clin Ther 2005;27:246–251.

In a patient with inoperable non–islet cell tumor hypoglycemia, fasting plasma glucose level was normalized with a combination of low-dose prednisone and recombinant HGH. This combination was more effective than high-dose monotherapy with either drug in reestablishing the IGF system and in long-term management for hypoglycemia, and did not cause any AEs.

48. (3) **Thorner MO** et al. Extrahypothalamic growth-hormone–releasing factor (GRF) secretion is a rare cause of acromegaly: Plasma GRF levels in 177 acromegalic patients. J Clin Endocrinol Metab 1984;59:846–849.

Ectopic GHRH secretion is a proven cause of acromegaly. In this study, plasma levels of GHRH were in the normal range in all of 177 acromegalic patients. Based on the results of the study, it appears that ectopic GHRH secretion is a rare cause of acromegaly.

49. (4) **Monica G** et al. Neuroendocrine tumors secreting growth hormone-releasing hormone: Pathophysiological and clinical aspects. Pituitary 2006;9:221–229.

This is an excellent review of diagnostic and treatment approaches to a patient with acromegaly due to ectopic GHRH secretion.

50. (3) **Biswal S** et al. Acromegaly caused by ectopic growth hormone: A rare manifestation of a bronchial carcinoid. Ann Thorac Surg 2008;85:330–332.

A patient with acromegaly is described where serum GH levels were elevated, her pituitary gland was normal on imaging, and a carcinoid was discovered in her lungs. Removal of the

carcinoid resulted in resolution of acromegaly and normalization of GH levels. The tumor stained heavily for GH by immunohistochemical staining.

51. (3) **Morley JE** et al. Choriocarcinoma as a cause of thyrotoxicosis. Am J Med 1976;60:1036–1040.

    Three patients with hyperthyroidism associated with choriocarcinoma are described. The decrease in severity of hyperthyroidism paralleled the decline in serum hCG levels. The serum from these patients contained TSH bioactivity that was related to hCG.

52. (4) **Hershman JM**. Human chorionic gonadotropin and the thyroid: Hyperemesis gravidarum and trophoblastic tumors. Thyroid 1999;9:653–657.

    This review describes that trophoblastic tumors, hydatidiform mole, and choriocarcinoma secrete very large amounts of hCG and cause hyperthyroidism when the serum hCG exceeds about 200 IU/ml. There is a correlation between the biochemical severity of hyperthyroidism and the serum hCG in these patients. Removal of the mole or effective chemotherapy of the choriocarcinoma cures the hyperthyroidism.

12

Genetics

Peter Kopp

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DEFINITION

Genetic components contribute to virtually all disorders, with the exception of simple trauma. Many chromosomal and monogenic disorders can now be explained at the molecular level, permitting to establish the diagnosis by mutational analysis (for selected examples, see Table 12.1) [1,12–16,19]. It is important to recognize that genetic and environmental *modifiers* may also strongly influence the phenotype in monogenic disorders, which simply present the least complex form in a continuum [7]. For example, siblings with identical mutations in the transcription factor PROP1, which lead to combined pituitary hormone deficiency (CPHD) [22], may have variable constellations of anterior pituitary hormone deficiencies, and the onset of the hormonal defects may differ [20]. In phenylketonuria, the development of the neurologic defects is dependent on the amount of phenylalanine in the diet. In *complex disorder*s, also referred to as *polygenic* or *multifactorial* disorders, several or multiple genes contribute to the pathogenesis, typically in conjunction with environmental and lifestyle factors such as in diabetes mellitus type 2 (Chapter 6) [4,7,10,51,52,54]. Genetic analyses are now greatly facilitated by the increasingly dense information about the human genome gleaned from the *Human Genome Project* (HGP) [7,13]. A first draft had been completed in 2000, and the HGP announced the completion of the DNA sequence for the last of the human chromosomes in 2006. The Personal Genome Project now aims at sequencing the genomes from multiple individuals and to associate them with health and physical data in order to obtain further insights into the genetic basis of human (patho)physiology. These developments are paralleled by fast-paced advances in next-generation sequencing technologies. It is anticipated that sequencing of the whole human genome of a human individual for a cost of $1,000 or less will become a reality within the next few years [9,81,82]. In addition to sequencing genomic DNA for the detection of mutations and variants, next-generation sequencing technologies can be used, among other applications, for the analysis of RNA expression and epigenetic modifications of the genome [82].

The HGP and the *HapMap* Project also facilitate the study of complex disorders [7]. The HapMap project has determined single nucleotide polymorphisms

Table 12.1. Molecular Basis of Selected Endocrine Disorders

Disorder/Phenotype	Chromosomal Defect		OMIM
Chromosomal disorders with endocrine manifestations			
Turner syndrome: Ovarian failure, short stature, autoimmune thyroid disease	45,XO		
Klinefelter syndrome: Hypogonadism, tall stature	47,XXY		
Prader-Willi syndrome: Short stature, obesity, hypogonadism	del15 q11–13 (Paternal copy) or Maternal uniparental disomy		176270
Disorder/Phenotype	**Gene**	**Inheritance**	**OMIM**
Hypothalamic and pituitary disorders			
CPHD (GH, PRL, TSH, LH, FSH)	PROP1	AR	601538
Short stature	GH	AR, AD	139250
Neurohypophyseal diabetes insipidus	AVP-NPII	AD, AR	192340
Obesity	Leptin receptor	AR	601007
Thyroid			
Congenital hypothyroidism with thyroid hypoplasia	PAX8	AD	167415
Bamforth-Lazarus syndrome:	TTF2 (FOXE1)	AR	602617
Congenital hypothyroidism, cleft palate, spiky hair			
Pendred syndrome: Sensorineural deafness, impaired iodide organification	PDS (SLC26A4)	AR	274600
Congenital hypothyroidism, TG defects	TG	AR	188450
Resistance to thyroid hormone	THRB	AD, (AR)	190160
Parathyroid and bone disorders			
Familial benign hypocalciuric hypercalcemia	CASR	AD	601199

(*Continued*)

Table 12.1. Molecular Basis of Selected Endocrine Disorders (*Continued*)

Disorder/Phenotype	Gene	Inheritance	OMIM
Familial hypoparathyroidism	CASR	AD	601199
Albright hereditary osteodystrophy	GNAS1	AD	103580
Adrenal gland			
Congenital adrenal hyperplasia, 21-hydroxlyase	CYP21	AR	201910
Glucocorticoid-remediable aldosteronism	CYP11B2-CYP11B1 fusion gene	AD	103900
Adrenal hypoplasia congenital, hypogonadism	DAX1 (NROB1)	X	300473
Pancreas			
MODY 1	HNF4α	AD	125850
MODY 2	GCK	AD (inactivating mutations)	125851
MODY 3	HNF1α	AD	600496
MODY 4, renal cysts	IPF1	AD	606392
MODY 5	HNF1β	AD	604284
MODY 6	NEUROD1	AD	606394
Pancreas agenesis	IPF1	AR	600733
Gonads			
Androgen insensitivity, AR inactivation	AR	AR	300068
Androgen insensitivity, 5α-reductase deficiency	SRD5A2	AR	607306
Aromatase deficiency, female genitalia with masculinization during puberty	CYP19A1	AR	107910
Water and salt metabolism			
Nephrogenic diabetes insipidus (X-linked form)	AVPR2	X	304800
Nephrogenic diabetes insipidus	AQP2	AR, AD	107777

Liddle syndrome: Hypokalemic metabolic acidosis, hypertension	SCNN1B or SCNN1G	AD	177200
Lipid metabolism			
Obesity	LEP	Leptin	164160
Familial hypercholesterinemia	LDLR	AD	606945
Tumor syndromes			
Multiple endocrine neoplasia 1: Parathyroid adenoma, pituitary adenoma, pancreas tumors	MEN1	AD	131100
Multiple endocrine neoplasia 2: (A) Medullary thyroid cancer, pheochromocytoma, parathyroid hyperplasia. (B) + ganglioneuromas	RET	AD	171400
von Hippel-Lindau disease: Renal carcinomas, pheochromocytomas, other tumors	VHL	AD	193300
Pheochromocytoma/Paraganglioma	MEN1, MEN2	AD or sporadic	131100, 171400
	NF1, VHL		162200, 193300
	SDHB, SDHC, SDHD		185470, 602413, 602690
	TMEM127		613403
Somatic mosaicism			
McCune-Albright syndrome: Precocious puberty, fibrous dysplasia, café-au-lait spots, hyperthyroidism	GNAS1	Mosaic somatic mutation acquired in early development	174800

(*Continued*)

Table 12.1. Molecular Basis of Selected Endocrine Disorders (*Continued*)

Disorder/Phenotype	Gene	Inheritance	OMIM
Complex syndromes			
Autoimmune polyglandular syndrome type 1: Adrenal insufficiency, hypoparathyroidism, candidiasis	AIRE	AR	240300
Disorder/Phenotype	**Genes/Loci**		**OMIM**
Complex disorders			
Diabetes mellitus type 1	HLA DR3/4-DQ201/0302, HLA DR4/4-DQ0300/03022, HLA DR3/3-DQ0201/0201 INS, PTPN22, IL2RA, CTLA4, IFIH1 *Multiple others*		222100
Diabetes mellitus type 2	PPARG, KCNJ11, TCF7L2 IGF2BP2, CDKAL1, SLC30A8, CDKN2A/B, JJEX, FTO, HNF1B *Multiple others*		125853

Note: This list only contains selected examples. In addition, the reader should be aware that the same or similar phenotype can be caused by mutations in other genes.

AD, autosomal dominant; AR, autosomal recessive; X, X-chromosomal; CPHD, combined pituitary hormone deficiency.

Modified from Kopp P. genetics, genomics, proteomics, and bioinformatics. In: Brook GD, Brown R (eds). Clinical Pediatric Endocrinology, 5th ed. Oxford. Blackwell Science; 205; 18-44, 2005. With permission.

(SNPs), variants that occur on average every 300 base pairs (bp) throughout the genome, in DNA samples from multiple individuals from several different ethnic backgrounds. Adjacent SNPs are inherited together as blocks, referred to as haplotypes, hence the name HapMap. These blocks can be identified by selected marker SNPs, so-called tag SNPs. The availability of this information permits to characterize a limited number of SNPs in order to determine the set of haplotypes present in an individual, for example, in cases and controls. This information has a significant impact on genome-wide association studies (GWAS), which search for associations of certain SNPs and haplotypes with complex disorders.

More recent insights into the structure of the human genome reveal a high degree of complexity. For example, certain regions of the genome, often containing numerous genes, can be duplicated once or even be present in multiple copies. These *copy number variations* (CNVs) tend to vary in a specific manner among different populations and are associated with hot spots of chromosomal rearrangements [11]. CNVs are thought to contribute to normal human variation as well as to disease through alterations in the dosage of a single gene or a set of contiguous genes.

Somatic mutations, that is, mutations that are limited to the affected tissue, in genes controlling cell growth, survival, and differentiation are key elements in the pathogenesis of benign and malignant tumors [7,13]. Moreover, many cancers are associated with a predisposition conferred by hereditary *germline* mutations. The multiple endocrine neoplasia syndromes 1 and 2 (MEN1 and MEN2) are excellent examples to illustrate this (Table 12.1) [67]. MEN2 also highlights the impact of genetic analysis for carrier detection in the clinical management of families with this tumor syndrome (Chapter 9) [67]. A thorough understanding of the molecular pathogenesis of cancer is also of paramount importance for the development of novel therapeutic modalities. For example, the mutations in the tyrosine kinase RET causing MEN2 [67], or the serine–threonine kinase B-Raf found frequently in papillary thyroid cancers, make them attractive targets for therapy with kinase inhibitors [68,86], a paradigm shown to be successful in chronic myelogenous leukemia by the specific inhibition of the Bcr–Abl tyrosine kinase through imatinib [63].

Numerous endocrine disorders have been elucidated at the molecular level [12–16,19]. For comprehensive overviews, and for the discussion of the principles of human genetics, DNA structure, and molecular biology analyses, which are beyond the scope of this chapter, the reader is referred to several comprehensive reviews and text books [7,13,15,80].

Genetic and genomic information is a key component of so-called personalized medicine, in which diagnosis, choice of therapy, and preventive measures are tailored to an individual based on differences in the genome [5,6,53,55]. For example, the management of carriers of *RET* gene mutations in kindreds affected by MEN2 or familial medullary thyroid cancer (FMTC) is, in part, dependent on the specific *RET* gene mutation, which display variable aggressivity [69].

ETIOLOGY

Mutations in DNA cause alterations and abnormal function in the encoded RNA and protein products, thereby leading to disease [2,3]. Mutations can occur randomly or through factors such as radiation and chemicals. Mutations occurring in the germline (sperm or oocytes) can be transmitted to progeny. If the germline is mosaic, a mutation can be transmitted to some offspring but not others. Mutations occurring during early development lead to somatic *mosaicism*, as illustrated by the McCune-Albright syndrome (MAS) [65,66]. Somatic mutations conferring a growth advantage to cells, or a decrease in apoptosis, can be

associated with neoplasia. Epigenetic alterations, for example, altered DNA methylation, are also frequently found in malignancies and can result in altered gene expression. With the exception of triplet nucleotide repeats [8], which can progressively expand, mutations are usually stable.

Structurally, mutations are extremely diverse [2]. They can involve the entire genome, as in triploidy, or gross numerical or structural alterations in chromosomes or individual genes [7,13]. Large deletions may affect a part of a gene, an entire gene, or several genes (*contiguous gene syndrome*). Somatic chromosomal rearrangements are found in many tumors. For example, rearrangements of the *RET* gene with several other genes can be found in a subset of papillary thyroid carcinomas [70]. Mutations affecting single nucleotides are referred to as *point mutations*. A mutation in the coding region leading to an amino acid substitution is referred to as *missense mutation*; a mutation resulting in a stop codon is a *nonsense mutation*. Small nucleotide deletions or insertions cause a shift of the reading frame (*frameshift*), and this typically results in an abnormal protein of variable length after the deletion. It is not sufficiently appreciated that mutations also occur in noncoding regions. Mutations in intronic sequences may destroy or create splice donor or splice acceptor sites, and mutations in regulatory sequences result in altered gene transcription.

EPIDEMIOLOGY

The frequency of monogenic disorders is highly variable [2]. Some monogenic disorders are extremely rare. Some recessive disorders occur predominantly in inbred populations or consanguineous matings. One should always consider the possibility of compound heterozygous mutations, that is, distinct mutations in the maternal and paternal copy of the same gene [62,64]. In many dominant and X-linked disorders, de novo mutations account for a significant fraction of cases. The rates for new mutations for autosomal dominant and X-linked disorders are estimated to be about approximately 10^{-5} to 10^{-6}/locus per generation. Other monogenic disorders are, however, relatively frequent. The classic examples include cystic fibrosis (Northern European populations), the thalassemias (Mediterranean, Southeast Asia), and sickle cell trait/disease (West Africa) [7]. It is generally thought that accumulation of these deleterious alleles in a population is due to a selective advantage in heterozygotes. For example, heterozygotes for the sickle cell mutation have a reduced morbidity and mortality from malaria because their erythrocytes provide a less favorable environment for *Plasmodium* parasites.

The distribution patterns of different genotypes in a population are the focus of population genetics [7]. If the frequency of an allele is known, and assuming that the population is in a state of equilibrium, the frequency of the genotypes can be determined (*Hardy-Weinberg law*). This is useful for the calculations of carrier frequencies, disease prevalence, and estimates of penetrance. The equilibrium can be modified by migration, new mutation(s), and genetic drift, that is, random fluctuations in allele frequencies in small populations.

The genetic epidemiology of complex disorders is challenging because of the fact that several or multiple loci may contribute to the phenotype and that it is influenced by multiple gene–gene interactions (also referred to as epistasis) and gene–environment interactions. In the endocrine field, this is impressively illustrated by our current understanding of the genetics of diabetes mellitus (Chapter 6) [51]. The neonatal and monogenic autosomal dominant forms of diabetes (MODY 1 to 6; maturity onset diabetes of the young) have been elucidated at the molecular level and are caused by severe mutations in genes that are essential for development and/or function of the pancreatic beta cell [50,53,55]. These mutations are

relatively rare in the population. In contrast, our knowledge about the genetic basis of diabetes mellitus type 2, although rapidly growing, remains more modest [51]. This may be explained by the difficulty in detecting alleles that are only contributing mildly to the phenotype, and the fact that these alleles are frequent in the general population [4]. Moreover, one should recognize that the clinical diagnosis of diabetes mellitus type 2 may encompass various entities of impaired insulin action and secretion and that the elucidation of the genetic components will require more homogeneous collections of patients.

PATHOPHYSIOLOGY

Very broadly, endocrine disorders can be categorized into four major types of conditions: (1) hormone excess [17], (2) hormone deficiency [26], (3) hormone resistance [23,27], and (4) tumors of endocrine glands without alterations of hormone secretion [13]. Numerous conditions in these categories have recently been explained by mutations in genes involved in growth or function of endocrine tissues, thereby leading to a better understanding of the pathophysiology at the molecular level and often providing a means for accurate diagnosis [13,15,17].

The functional consequences of mutations can be broadly classified as gain-of-function and loss-of-function mutations [7,28]. Gain-of-function mutations are typically dominant. In contrast, inactivating mutations are usually recessive, and affected individuals are homozygous or compound heterozygous, that is, carrying two different mutant alleles in the same gene, for the disease-causing mutations. Alternatively, a mutation in a single allele can result in *haploinsufficiency*, a situation in which one normal allele is not sufficient to maintain a normal phenotype, and this may result in dominant inheritance [7]. Haploinsufficiency is a frequently observed mechanism in diseases associated with mutations in transcription factors or rate-limiting enzymes [18,34]. Mutation in a single allele can also result in loss of function through a dominant-negative effect [23,49]. In this case, the mutated allele interferes with the function of the normal gene product by one of several different mechanisms: (1) The mutant protein may interfere with other members of a multimeric protein complex, as illustrated by mutations in aquaporin 2 in the autosomal dominant form of nephrogenic diabetes mellitus because [44,49]; (2) the mutant protein may occupy binding sites on proteins or promoter response elements, as illustrated by thyroid hormone resistance [23]; or (3) the mutant protein can be cytotoxic as, for example, in autosomal dominant neurohypophyseal diabetes insipidus [46], in which the abnormally folded proteins are trapped within the endoplasmic reticulum thereby leading to progressive destruction of vasopressin-secreting neurons.

DIAGNOSIS

Approach to the Patient

It cannot be emphasized enough that a careful clinical examination with thorough phenotyping, using appropriate biochemical and ancillary tests, is absolutely essential [71]. One should always be aware of the possibility of *phenocopies*, that is, a phenotype that is identical or similar to the suspected disorder but that has a distinct genetic or nongenetic pathogenesis [24]. For example, obesity may be simply the consequence of lifestyle factors, but it can also be caused by several Mendelian defects (Chapter 34) [56,59]; dyslipidemias may be due to monogenic defects or reflecte complex disorders [60,61], and lipodystrophies may have a genetic or nongenetic origin such as therapy with highly active antiviral therapy [57]. The presence of phenocopies in a family can be problematic because it can confound linkage studies and genetic testing.

The family history is of great importance for the recognition of a hereditary component. It should include the establishment of a pedigree of the nuclear or the

extended family [7]. The history, in combination with the pedigree, may become of practical relevance for genetic counseling, carrier detection, quantitative risk estimation for individuals within the kindred, or early intervention and prevention of a disease in relatives of the index patient(s). However, a precise risk estimate is often only possible after genetic testing. The ethnic background is relevant since certain alleles are more common in certain populations.

When evaluating relatives of an index patient with a genetic disorder, the phenomena of variable *expressivity* and *incomplete penetrance* should always be considered [7,43]. Penetrance is complete if all carriers of a given mutation express the phenotype and *incomplete* if some individuals do not express the phenotype. Incomplete penetrance is characterized by a disease phenotype skipping generations with unaffected carriers transmitting the mutant gene. Expressivity describes the degree to which a phenotype is expressed, the *phenotypic spectrum*. The mechanisms resulting in variable expressivity and incomplete penetrance include the need for modifiers such as *genetic background*, gender, and environmental factors, emphasizing again that these factors do not only play a prominent role in complex disorders but also in Mendelian traits.

Phenotypic heterogeneity may also arise from differences in the effect of mutations at different sites within the same gene. This is well illustrated by mutations in the androgen receptor (AR); mild mutations may cause epispadias, while severe inactivation of the receptor results in complete resistance to testosterone with testicular feminization [42]. Distinct mutations in the same gene may, depending on the location and functional consequences, result in distinct phenotypes. For example, mutations in the gene encoding the nuclear lamin A protein can result in familial partial lipodystrophy (Dunnigan) or Emery-Dreifuss muscular dystrophy, among other phenotypes [58].

Information about Genetic Disorders

If a clinician seeks information about a genetic disorder, or a particular nonsyndromic or syndromic phenotype, consultation of the continuously updated *Online Mendelian Inheritance in Man* (OMIM) catalog (http://www.ncbi.nlm.nih.gov/omim/) is an excellent starting point (Table 12.2). OMIM lists several thousand genetic disorders, and it provides information about the clinical phenotype, the molecular basis, allelic variants, relevant animal models, and pertinent references. Embedded links to other electronic resources (e.g., PubMed for literature searches, GenBank for sequence information, databases compiling gene mutations) provide relevant information for both clinicians and basic researchers. Selected additional databases that provide relevant information are listed in Table 12.2, and several recent textbook chapters discuss the genetic etiology and mechanisms underlying endocrine disorders [13,15,19].

Genetic Counseling

Consultation with a medical geneticist and/or medical counselor is often indicated for the management of patients with a sporadic or inherited genetic disorder [72–75]. This is helpful for diagnostic purposes [53,55], the identification of management issues [69], and determination of genetic risk in relatives and offspring [38]. It may also be of importance for appropriate psychological support.

Genetic Testing

Genetic testing aims at detecting (molecular) alterations associated with inherited or sporadic disorders. Depending on the test, it will be performed with sources such as metaphase chromosomes, genomic or mitochondrial DNA, RNA, chromosomes, proteins, or metabolites [7]. Different clinically relevant forms of genetic testing include preimplantation testing, prenatal testing, newborn

screening, carrier screening, diagnostic testing, paternity/maternity tests, and zygosity tests. Research and investigational tests are important for improving the understanding of rare conditions or developing clinical tests, but the results may not always be available to the patient and the physician.

Diagnostic molecular testing should be performed to confirm, or exclude, a diagnosis relying on clinical evaluation and biochemical testing. Information of the exact genetic defect can be of value because it can provide certainty about the diagnosis, it may allow prediction about the clinical course, and serve as a basis for genetic counseling and molecular diagnosis in other family members or future pregnancies.

Predictive testing or carrier screening permits the identification of individuals who are carriers of a mutation and, similarly, to determine who is not at risk because of absence of the mutation. This is exemplified by the analysis of children of families with MEN2 (Chapter 9) [67,69]. Similarly, genetic testing is increasingly important in the management of patients with sporadic and familial pheochromocytomas (Chapter 10) [31,33].

If genetic testing is considered, the proband and the family should be carefully informed about the potential consequences of positive results, including psychological distress and the possibility of discrimination. Importantly, the Genetic Information Nondiscrimination Act (GINA), signed into law in 2008, aims at protecting individuals against the misuse of genetic information for health insurance and employment [78]. Equally important is the discussion of the meaning of negative results. This should also include a discussion of false negative or inconclusive results and technical limitations of the tests. For these reasons, genetic testing should only be performed after obtaining informed consent [77]. Genetic testing in children poses additional ethical issues. Ethical guidelines published by the American Society of Human Genetics and the American Academy of Pediatrics address aspects that should be considered when testing children and adolescents [76,79]. Unless the analyses may provide relevant insights into the molecular pathogenesis of a disorder, it should be limited to situations in which the results may have an impact on the medical management and it requires informed consent by the parents. If there is no apparent benefit, testing should usually be deferred until the patient can consent independently. This is, for example, of relevance in devastating disorders such as Huntington disease.

Sample Collection

Sample collection is dependent on the nature of the test and must be performed according to instructions by the laboratory performing the analysis [83]. If a disease-causing mutation is expected due to germline transmission, DNA is most commonly collected from nucleated blood cells, and typically, 5 ml of EDTA is sufficient for this purpose. In the case of somatic mutations, which are limited to the affected tissue, an adequate sample of the lesion will serve for the extraction of DNA or RNA. RNA degrades very quickly, and the sample serving for its extraction has to be frozen or immersed in special solutions immediately. For cytogenetic analyses, cells are often collected from peripheral blood or buccal smears, but other tissues can also serve as source. Biochemical tests continue to play an important role in the analysis of metabolic disorders and will require appropriate collection of plasma, serum, or urine. For the detection of pathogens, the material to be analyzed will vary and may include blood, cerebrospinal fluid, solid tissues, sputum, or fluid obtained through bronchoalveolar lavage.

Laboratories Performing Genetic Tests

Genetic testing is now readily available through commercial laboratories for a large number of endocrine disorders. Commonly used mutational analyses

include, among others, the menin gene (MEN1) [67], the RET gene (MEN2) [69], the CYP21A2 gene (congenital adrenal hyperplasia [CAH]) [32,75], the genes causing the various forms of MODY [55], the genes associated with pheochromocytomas/paragangliomas [31,36], the AVPR2 gene (nephrogenic diabetes insipidus) [45], and the AVP-NPII gene (autosomal dominant neurohypophyseal diabetes insipidus) [44]. For rare disorders, the test may only be performed in a specialized laboratory.

The *GeneTests* web site (http://www.ncbi.nlm.nih.gov/sites/GeneTests/servlet/access), a publicly funded medical genetics information resource, contains a laboratory directory that is useful for identifying CLIA (Clinical Laboratory Improvement Amendments)-approved laboratories offering testing for inherited disorders (Table 12.2). For other rare disorders, the test may only be available through research laboratories.

Practical Limitations of Genetic Testing

The public, as well as many physicians, are not aware of certain conceptual and technical challenges that may be associated with genetic testing. Asides from issues related to sample management and technical errors, they include, among others, the possibility of *locus heterogeneity*, *allelic heterogeneity*, and the possibility of *polymorphisms* [7].

Locus heterogeneity, also referred to as nonallelic heterogeneity, designates the fact that an identical or highly similar phenotype may result from mutations in different genes located at different loci within the genome [21,25,29,30,35,39–41]. For example, congenital hypothyroidism due to defects in thyroid hormone synthesis within the thyrocyte can be caused by mutations in several genes encoding proteins that exert key steps in this process (NIS = sodium/iodide symporter; PDS/SLC26A4 = pendrin; TPO = thyroid peroxidase; TG = thyroglobulin; DUOX2 = thyroid oxidase 2; DUOXA2 = DUOX maturation factor 2; DEHAL1 = dehalogenase 1) [25,26]. Similarly, defects in the growth hormone axis can be located in multiple different genes [21]. In such a situation, genetic testing is complex and expensive because several different genes need to be analyzed. Locus heterogeneity can also cause a problem for linkage studies because it can reduce the ability to identify disease loci [37,47,48].

Allelic heterogeneity indicates that different mutations in the same gene can cause an identical or similar phenotype. For example, there are currently more than 1,800 known mutations in the CFTR gene (cystic fibrosis mutation database: http://www.genet.sickkids.on.ca/cftr/). While an initial analysis will focus on mutations that are particularly frequent, a negative result does not exclude the presence of a mutation elsewhere in the gene. One should also be aware that mutational analyses are usually focusing on the coding region of a gene without considering regulatory and intronic regions. Given that disease-causing mutations may be located outside the coding regions, any negative results may have to be interpreted with caution. These challenges will be easier to address with the more comprehensive and cheaper sequencing technologies. It is now possible to enrich selected genomic regions, several genes, or even the whole exome (i.e., all coding exons within the genome) and submit them to sequence analysis with next-generation sequencing platforms. However, the bioinformatic analysis of the generated sequences remains a challenging task.

Polymorphisms are sequence variations that may occur more or less frequently in the genome of the general population. Many of them do not have any functional consequences; others may lead to subtle functional alterations in the gene product (mRNA or protein). While frequently occurring polymorphisms can be detected relatively easily by assessing their presence in a cohort of unrelated

Table 12.2. Selected Databases

Site	Content	URL
Online Mendelian Inheritance in Man	Catalog of human genetic disorders	http://www.ncbi.nlm.nih.gov/omim/
National Center for Biotechnology Information	Portal with links to genomic databases, PubMed, OMIM, and educational online resources	http://www.ncbi.nlm.nih.gov/
GeneTests	Directory of laboratories offering genetic testing	http://www.ncbi.nlm.nih.gov/sites/GeneTests/servlet/access
GeneCards	A database of human genes and their role in disease	http://www.genecards.org/
American College of Medical Genetics	Portal with databases relevant for the diagnosis, treatment, and prevention of genetic diseases	http://www.acmg.net/
Chromosomal Variation in Man	Catalog of chromosomal disorders	http://www.wiley.com/legacy/products/subject/life/borgaonkar/access.html
Mitochondrial Disorders	Catalog of disorders associated with mitochondrial DNA mutations	http://neuromuscular.wustl.edu/mitosyn.html
DNA Repeat Sequences and Disease	Catalog of disorders associated with DNA repeats	http://neuromuscular.wustl.edu/mother/dnarep.htm
National Organization for Rare Disorders	Catalog of rare disorders including clinical presentation, diagnostic evaluation, and treatment	http://www.rarediseases.org/
HapMap Project Web	Portal to the International Haplotype Map Project	http://www.hapmap.org
Genome-Wide Association Studies	Portal on GWAS with information on completed studies on numerous phenotypes	http://gwas.nih.gov

normal individuals, rare polymorphisms require rigorous functional analyses in vitro in order to distinguish them from disease-causing mutations.

Treatment

Given the broad spectrum of disorders with a genetic component or a genetic basis, a discussion of the appropriate treatments is beyond the scope of this chapter. Similarly, a discussion of gene therapy, the transfer of genetic material into a patient, cannot be discussed here [87]. Molecular genetics already has a significant impact on the treatment of human disease. Peptide hormones (*insulin*, *growth hormone*, *erythropoietin*, *thyrotropin*, *parathyroid hormone*), growth factors (*colony-stimulating factors*), cytokines (*interferons*), enzymes (*α-1,4 glucosidase*), or vaccines (*hepatitis B*) can now be produced in large amounts using recombinant DNA technology. Targeted modification of these peptides provides the practitioner with improved therapies, as illustrated by genetically modified insulin analogs with altered kinetics [85]. The elucidation of the molecular pathogenesis is of great importance for the development of novel therapeutic modalities. This is, for example, illustrated by inhibitors targeting intracellular kinases and vascular growth factors, which play a growing role in the therapy of advanced endocrine tumors such as medullary, papillary, and follicular carcinomas [86]. As another example, patients with parathyroid cancer can now be treated with inhibitors of the calcium-sensing receptor (CASR) [84].

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Note: *Because of space constraints, the bibliography contains predominantly reviews and only selected references illustrating key concepts or recent novel contributions.*

Genetics and Genomic Medicine

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