Chapter 96: Thyroid Disorders

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CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 20, Thyroid Disorders.

KEY CONCEPTS

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1. Thyrotoxicosis is most commonly caused by Graves' disease, which is an autoimmune disorder in which thyroid-stimulating antibody (TSAb) directed against the thyrotropin receptor elicits the same biologic response as thyroid-stimulating hormone (TSH).

2. Hyperthyroidism may be treated with antithyroid drugs such as methimazole (MMI) or propylthiouracil (PTU), radioactive iodine (RAI: sodium iodide-131 [^{131}I]), or surgical removal of the thyroid gland; selection of the initial treatment approach is based on patient characteristics such as age, concurrent physiology (eg, pregnancy), comorbidities (eg, chronic obstructive lung disease), and convenience.

3. MMI and PTU reduce the synthesis of thyroid hormones and are similar in efficacy, although their dosing ranges differ by 20-fold. Overall, PTU has a greater incidence of side effects. Agranulocytosis is a rare but severe adverse effect associated with both medications.

4. Response to MMI and PTU is seen in 4 to 6 weeks and therefore β-blocker therapy may be concurrently initiated to reduce adrenergic symptoms. Maximal response is typically seen in 4 to 6 months; treatment usually continues for 1 to 2 years, and therapy is monitored by clinical signs and symptoms and by measuring the serum concentrations of TSH and free thyroxine (FT_4).

5. Adjunctive therapy with β-blockers controls the adrenergic symptoms of thyrotoxicosis but does not correct the underlying disorder; iodine may also be used adjunctively in preparation for surgery and acutely for thyroid storm.

6. Many patients choose to have ablative therapy with ^{131}I rather than undergo repeated courses of MMI or PTU treatment; most patients receiving RAI eventually become hypothyroid and require thyroid hormone supplementation.

7. Hypothyroidism is most often due to an autoimmune disorder known as *Hashimoto's thyroiditis*.

8. The drug of choice for replacement therapy in hypothyroidism is levothyroxine.

9. Studies of combination therapy with levothyroxine and liothyronine have not shown reproducible benefits. This approach to the treatment of hypothyroidism requires further study.

10. Monitoring of levothyroxine replacement therapy is achieved by observing clinical signs and symptoms and by measuring the serum TSH level. An elevated TSH indicates under-replacement; a suppressed TSH indicates over-replacement.

BEYOND THE BOOK

BEYOND THE BOOK

To get a basic understanding of hyperthyroidism and hypothyroidism, visit the Websites of National Institutes of Health and National Institute of Diabetes and Digestive and Kidney Diseases for a quick overview:

https://www.niddk.nih.gov/health-information/endocrine-diseases/hyperthyroidism

https://www.niddk.nih.gov/health-information/endocrine-diseases/hypothyroidism

INTRODUCTION

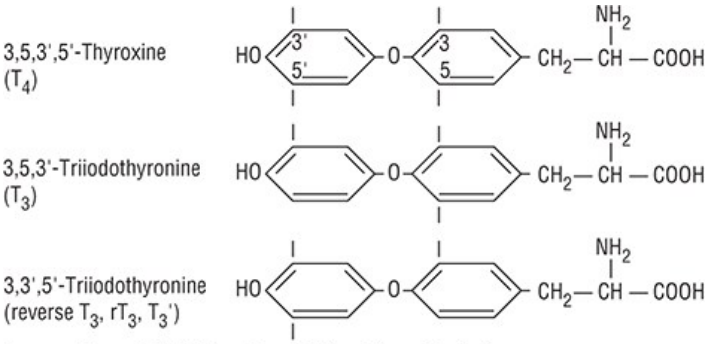
Thyroid hormones affect the function of virtually every organ system. In a child, thyroid hormone is critical for normal growth and development. In an adult, the major role of thyroid hormone is to maintain metabolic stability. Substantial reservoirs of thyroid hormone in the thyroid gland and blood provide constant thyroid hormone availability. In addition, the hypothalamic-pituitary-thyroid axis is exquisitely sensitive to small changes in circulating thyroid hormone concentrations, and alterations in thyroid hormone secretion maintain peripheral free thyroid hormone levels within a narrow range. Patients seek medical attention for evaluation of symptoms due to abnormal thyroid hormone levels or because of diffuse or nodular thyroid enlargement.

Thyroid Hormone Synthesis

The thyroid hormones thyroxine (T_4) and triiodothyronine (T_3) (Fig. 96-1) are formed within thyroglobulin (TG), a large glycoprotein synthesized in the thyroid cell. Because of the unique tertiary structure of this glycoprotein, iodinated tyrosine residues present in TG are able to bind together to form active thyroid hormones.

FIGURE 96-1

Structure of thyroid hormones.

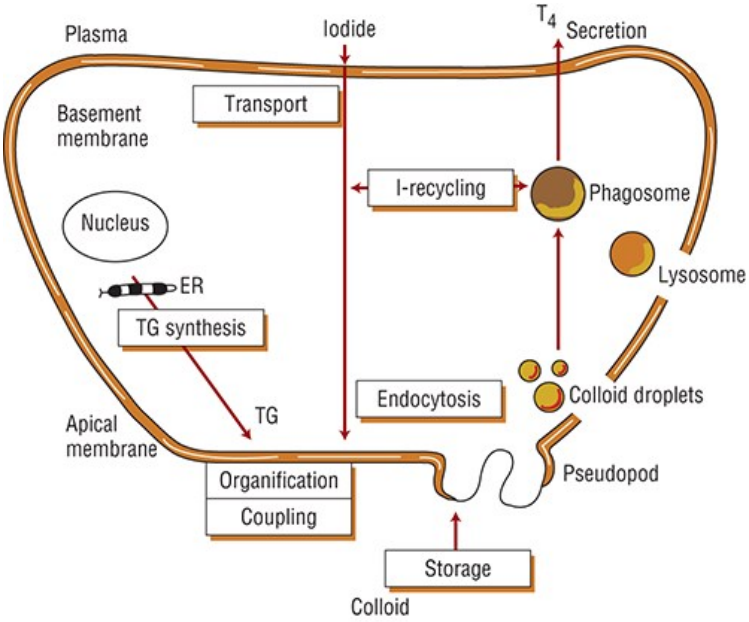


Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Iodide is actively transported through the basolateral membrane via a Na^+/I^- symporter from the extracellular space into the thyroid follicular cell against an electrochemical gradient, driven by the coupled transport of sodium.[1] Structurally related anions such as thiocyanate (SCN^-), perchlorate (ClO_4^-), and pertechnetate (TcO_4^-) are competitive inhibitors of iodine transport.[1] In addition, bromine, fluorine, and, under certain circumstances, lithium block iodide transport into the thyroid (Table 96-1). Inorganic iodide that enters the thyroid follicular cell is ushered through the cell to the apical membrane, where it is transported into the follicular lumen by pendrin, and possibly other transport proteins.[1] Located on the luminal side of the apical membrane, thyroid peroxidase oxidizes iodide and covalently binds the organified iodide to tyrosine residues within TG (Fig. 96-2). It is interesting that although salivary glands and the gastric mucosa are able to actively transport iodide, they are unable to effectively incorporate iodide into proteins, given the lack of similar oxidizing machinery.

FIGURE 96-2

Thyroid hormone synthesis. Iodide is transported from the plasma, through the cell, to the apical membrane, where it is organified and coupled to the thyroglobulin (TG) synthesized within the thyroid cell. Hormone stored as colloid re-enters the cell through endocytosis and moves back toward the basal membrane, where thyroxine (T_4) is secreted.



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

TABLE 96-1

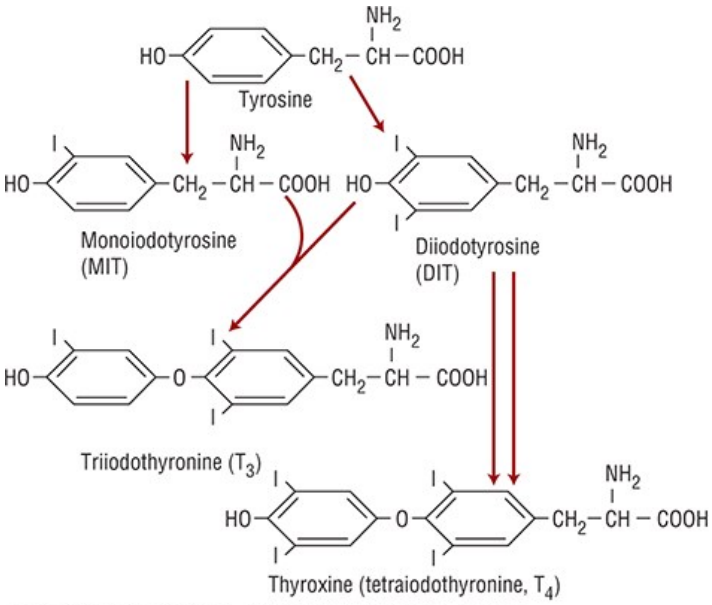
Thyroid Hormone Synthesis and Secretion Inhibitors

Mechanism of Action	Substance
Blocks iodide transport into the thyroid	• Bromine • Fluorine • Lithium
Impairs organification and coupling of thyroid hormones	• Thionamides • Sulfonamide • Salicylamide • Antipyrine
Inhibits thyroid hormone secretion	Iodide (large doses) Lithium

The iodinated tyrosine residues monoiodotyrosine (MIT) and diiodotyrosine (DIT) combine to form iodothyronines (Fig. 96-3). Thus, two molecules of DIT combine to form T_4, whereas MIT and DIT constitute T_3. In addition to its role in iodine organification, the hemoprotein thyroid peroxidase also catalyzes the formation of iodothyronines (coupling).

FIGURE 96-3

Scheme of coupling reactions. After tyrosine is iodinated to form monoiodotyrosine (MIT) or diiodotyrosine (DIT) (organification of the iodine), MIT and DIT combine to form triiodothyronine (T_3) or two molecules of DIT combine to form thyroxine T_4 (coupling).



Iodine deficiency causes an increase in the MIT:DIT ratio in TG and leads to a relative increase in the production of T_3:T_4. Because T_3 is more potent than T_4, the increase in T_3 production in iodine-deficient areas may be beneficial. The thionamide drugs used to treat hyperthyroidism inhibit thyroid peroxidase and thus block thyroid hormone synthesis.

Thyroglobulin is stored in the follicular lumen and must reenter the cell, where the process of proteolysis liberates thyroid hormone into the bloodstream. Thyroid follicles active in hormone synthesis are identified histologically by columnar epithelial cells lining a follicular lumen, which is depleted of colloid. Inactive follicles are lined by cuboidal epithelial cells and are replete with colloid. Both iodide and lithium block the release of preformed thyroid hormone, through poorly understood mechanisms.

T_4 and T_3 are transported in the bloodstream primarily by three proteins: (1) thyroxine-binding globulin (TBG), (2) transthyretin (TTR; also known as TBPA, thyroxine-binding prealbumin), and (3) albumin. It is estimated that 99.96% of circulating T_4 and 99.5% of T_3 are bound to these proteins. However, only the unbound (free) thyroid hormone is able to diffuse into the cell, elicit a biologic effect, and regulate thyroid-stimulating hormone (TSH; also known as *thyrotropin*) secretion from the pituitary. Multiple functions have been ascribed to these transport proteins, including (a) assuring minimal urinary loss of iodide, (b) providing a mechanism for uniform tissue distribution of free hormone, and (c) transporting hormone into the central nervous system (CNS).

Whereas T_4 is secreted solely from the thyroid gland, less than 20% of T_3 is produced in the thyroid. The majority of T_3 is formed from the breakdown of T_4 catalyzed by the 5'-monodeiodinase enzymes found in extrathyroidal peripheral tissues. Because the binding affinity of nuclear thyroid hormone receptors (TRs) is 10 to 15 times higher for T_3 than for T_4, the deiodinase enzymes play a pivotal role in determining overall metabolic activity. Three different monodeiodinase enzymes are present in the body. Of the enzymes that catalyze 5'-monodeiodination, type I enzymes are present in peripheral tissues such as the liver and kidney, whereas type II enzymes are found in the CNS, pituitary, and thyroid. Type III enzymes, found in the placenta, skin, and developing brain, inactivate T_4 and T_3 by deiodinating the inner ring at the 5 position. The principal characteristics of these enzymes are listed in Table 96-2. T_4 may also be acted on by the enzyme 5'- monodeiodinase to form reverse T_3, but this accounts for a small component of hormone metabolism. Polymorphisms in the deiodinase genes may prove to be of clinical significance. For example, a polymorphism in

the type I deiodinase leading to increased activity seems to be associated with an increased circulating ratio of free T_3 to free T_4.[2] Reverse T_3 has no known biological activity. T_3 is removed from the body by deiodinating degradation and through the action of sulfotransferase enzyme systems converting to T_3 sulfate and 3,3-diiodothyronine sulfates, thus facilitating enterohepatic clearance. Thyronamines are derivatives of thyroid hormones that are present in low concentrations in human serum. The most studied thyronamine, 3-iodothyronamine, can theoretically be made from T_4 by decarboxylation and deiodination. Administration of pharmacologic amounts of 3-iodothyronamine to animals has profound effects on temperature regulation and cardiac function and shifts fuel metabolism from carbohydrates to lipids. However, a possible physiologic role for thyronamines has yet to be determined, although altered levels may be associated with some disease states.

TABLE 96-2

Properties of Iodothyronine 5′-Deiodinase Isoforms

Property	Type I	Type II	Type III
Susceptibility to propylthiouracil	High	Low	Low
Tissue localization	Thyroid, liver, kidney	Pituitary, thyroid, CNS, brown adipose tissue	Placenta, developing brain, skin
Preferred substrate	rT_3 and T_3	T_4 and rT_3	T_3 and T_4
Physiologic or pathophysiologic role	Clearance of rT_3 and T_3, the predominant extrathyroidal source of T_3 in hyperthyroidism	Intracellular T_3 production, especially for the brain in hypothyroidism or iodine deficiency, and maintenance of plasma T_3	Clearance of T_3 and T_4
Developmental expression	Expressed latest in development; predominant deiodinase in adult	Expressed second; especially high in brain and brown adipose tissue	Expressed first; high in developing brain; may be important for fetal thyroid hormone metabolism

rT_3, reverse T_3; T_3, triiodothyronine; T_4, thyroxine.

Thyroid Hormone Regulation and Action

The growth and function of the thyroid are stimulated by activation of the thyrotropin receptor by TSH.[3] The receptor belongs to the family of G-protein–coupled receptors. The thyrotropin receptor is coupled to the α subunit of the stimulatory guanine-nucleotide–binding protein (Gsα), activating adenylate cyclase and increasing the accumulation of cyclic adenosine monophosphate. Through this mechanism, TSH stimulates the expression of Na^+/I^- symporter, TG, and thyroid peroxidase genes as well as increases apical iodide efflux. Somatic activating mutations in the receptor are commonly seen in autonomously functioning thyroid nodules.[4] Rarely, germline-activating mutations of the TSH receptor have been reported in kindreds with Leclere syndrome, and thyrotoxicosis can result from germline-activating mutations in G-protein signaling in McCune–Albright syndrome. Conversely, thyrotropin resistance results from point mutations that prevent TSH binding, leading to abnormalities in the thyrotropin receptor–adenylate cyclase system and congenital hypothyroidism.[3] Individuals with this abnormality have high levels of TSH but decreased TG levels and a normal or small thyroid gland.

Thyroid hormone nuclear receptors regulate the transcription of target genes in the presence of physiologic concentrations of T_3.[3] Unlike most other nuclear receptors, TRs also actively regulate gene expression in the absence of hormone, typically resulting in an opposite effect. TRs translocate from

the cytoplasm to the nucleus, interact in the nucleus with T_3, and target genes and other proteins required for basal and T_3-dependent gene transcription. TRs exist in several isoforms, including TRβ1, TRβ2, and TRα1.[3] Thyroid hormone has different actions in different tissues based on the tissue-specific expression of the different TR isoforms. There is interest in developing thyroid hormone analogs that selectively activate specific TR isoforms. Such agents could theoretically have targeted desirable effects such as stimulating energy expenditure without having adverse effects on other tissues.[5]

The production of thyroid hormone is regulated in two main ways. First, thyroid hormone is regulated by TSH secreted by the anterior pituitary. The secretion of TSH is itself under negative feedback control by the circulating level of free thyroid hormone and the positive influence of hypothalamic thyrotropin-releasing hormone (TRH). Second, extrathyroidal deiodination of T_4 to T_3 is regulated by a variety of factors including nutrition, nonthyroidal hormones, ambient temperatures, drugs, and illness.

HYPERTHYROIDISM AND THYROTOXICOSIS

Thyrotoxicosis results when tissues are exposed to excessive levels of T_4, T_3, or both.[6] Hyperthyroidism, which is one cause of thyrotoxicosis, refers specifically to overproduction of thyroid hormone by the thyroid gland.

EPIDEMIOLOGY—THYROTOXICOSIS

In the National Health and Nutrition Examination Survey (NHANES) III, 0.7% of those surveyed who were not taking thyroid medications and had no history of thyroid disease had subclinical hyperthyroidism (TSH less than 0.1 mIU/L, and T_4 normal), and 0.5% had “clinically significant” hyperthyroidism (TSH less than 0.1 mIU/L, and T_4 more than 13.2 mcg/dL [170 nmol/L]).[7] The prevalence of suppressed TSH values peaks in people aged 20 to 39, declines in those 40 to 79, and increases again in those 80 or older. Abnormal TSH levels were more common among women than among men.

ETIOLOGY AND PATHOPHYSIOLOGY—THYROTOXICOSIS

If the clinical history and examination do not provide pathognomonic clues to the etiology of the patient’s thyrotoxicosis, measurement of the radioactive iodine uptake (RAIU) is critical in the evaluation (Table 96-3). The normal 24-hour RAIU ranges from 10% to 30% with some regional variation that is due to differences in iodine intake. An elevated RAIU indicates endogenous hyperthyroidism; that is, the patient’s thyroid gland is actively overproducing T_4, T_3, or both. Conversely, a low RAIU in the absence of iodine excess indicates that high levels of thyroid hormone are not a consequence of thyroid gland hyperfunction but are likely due to thyroiditis or hormone ingestion. The importance of differentiating endogenous hyperthyroidism from other causes of thyrotoxicosis lies in the widely different prognosis and treatment of the diseases in these two categories. Therapy of thyrotoxicosis associated with thyroid hyperfunction is mainly directed at decreasing the rate of thyroid hormone synthesis, secretion, or both. Such measures are ineffective in treating thyrotoxicosis that is not the result of endogenous hyperthyroidism because hormone synthesis and regulated hormone secretion are already at a minimum.

Causes of Thyrotoxicosis Associated with Suppressed RAIU

Subacute Thyroiditis

Painful subacute (granulomatous or de Quervain) thyroiditis often develops after a viral syndrome, but rarely has a specific virus been identified in thyroid parenchyma. A genetic predisposition exists, with a markedly higher risk for developing subacute thyroiditis for patients with HLA-Bw35. Systemic symptoms often accompany the syndrome, including fever, malaise, and myalgia, in addition to those symptoms due to thyrotoxicosis. Typically, patients complain of severe pain in the thyroid region, which often extends to the ear on the affected side. With time, the pain may migrate from one side of the gland to the other. On physical examination, the thyroid gland is firm and exquisitely tender. Signs of thyrotoxicosis are present.[17]

Thyroid function tests typically run a triphasic course. Initially, serum T_4 levels are elevated due to the release of preformed thyroid hormone from disrupted follicles. The 24-hour RAIU during this time is less than 2% due to thyroid inflammation and TSH suppression by the elevated T_4 level. As the

disease progresses, intrathyroidal hormone stores are depleted, and the patient may become mildly hypothyroid with an appropriately elevated TSH level. During the recovery phase, thyroid hormone stores are replenished, and serum TSH concentration gradually returns to normal. Recovery is generally complete within 2 to 6 months. Most patients remain euthyroid, and recurrences of painful thyroiditis are extremely rare. The patient with painful thyroiditis should be reassured that the disease is self-limited and is unlikely to recur. Thyrotoxic symptoms may be relieved with β-blockers. nonsteroidal anti-inflammatory drugs (NSAIDs) will usually relieve the pain. Occasionally, prednisone (30-40 mg daily) must be used to suppress the inflammatory process. Antithyroid drugs (ATD) are not indicated because they will not be effective as they do not decrease the release of preformed thyroid hormone.

Painless Thyroiditis

Painless (silent and lymphocytic) thyroiditis is a common cause of thyrotoxicosis and may represent up to 15% of cases of thyrotoxicosis in North America. When lymphocytic thyroiditis develops during the first 12 months after the end of pregnancy, the condition is also called *postpartum thyroiditis.* The etiology is not fully understood and may be heterogeneous, but evidence indicates that autoimmunity underlies most cases. There is an increased frequency of HLA-DR3 and DR5 in patients with painless thyroiditis; non-endocrine autoimmune diseases are also more common. Histologically, diffuse lymphocytic infiltration is generally identified. The triphasic course of this illness mimics that of subacute thyroiditis. Most patients present with mild thyrotoxic symptoms. Lid retraction and lid lag are present, but exophthalmos is absent. The thyroid gland may be diffusely enlarged, but thyroid tenderness is absent.

The 24-hour RAIU will typically be suppressed to less than 2% during the thyrotoxic phase of painless thyroiditis. Anti-TG and antithyroid peroxidase antibody (anti-TPOAb) levels are elevated in more than 50% of patients. Patients with mild hyperthyroidism and painless thyroiditis should be reassured that they have a self-limited disease, although patients with postpartum thyroiditis may experience a recurrence of the disease with subsequent pregnancies. As with other thyrotoxic syndromes, adrenergic symptoms may be ameliorated with propranolol or metoprolol. ATDs, which inhibit new hormone synthesis, are not indicated because they do not decrease the release of preformed thyroid hormone. A small proportion of patients may have recurrent episodes of thyroiditis or may develop permanent hypothyroidism.[17]

Exogenous Thyroid Hormone

Thyrotoxicosis factitia is hyperthyroidism due to ingestion of thyroid hormone. This category includes hyperthyroidism produced by the intentional ingestion of exogenous thyroid hormone. Obesity is the most common non-thyroidal disorder for which thyroid hormone is inappropriately used, but thyroid hormone has been used for almost every conceivable problem from menstrual irregularities and infertility to hypercholesterolemia and baldness. There is little evidence to suggest that treatment with thyroid hormone is beneficial for any of these conditions in euthyroid individuals.[18] Thyrotoxicosis factitia can also occur when too large a dose of thyroid hormone is used to treat conditions in which it is likely to be beneficial, such as differentiated thyroid carcinoma. In addition to this iatrogenic cause, thyrotoxicosis factitia may occur after accidental pediatric ingestion or pharmacy error. Thyrotoxicosis factitia may also be caused by the purposeful and secretive ingestion of thyroid hormone by patients (usually with a healthcare background) who wish to obtain attention or lose weight.

Thyroid hormone may also be accidentally ingested in food sources. Reports of thyrotoxicosis in Minnesota and Nebraska in the 1980s were attributed to ingestion of ground beef contaminated by bovine thyroid glands. More recently thyrotoxicosis due to porcine thyroid tissue in meat products has been reported in Spain and Uruguay.

Thyrotoxicosis factitia should be suspected in a thyrotoxic patient without evidence of increased hormone production, thyroidal inflammation, or ectopic thyroid tissue. The RAIU is at low levels because the patient's thyroid gland function is suppressed by the exogenous thyroid hormone. Measurement of plasma TG is a valuable laboratory aid in the diagnosis of thyrotoxicosis factitia. TG is normally secreted in small amounts by the thyroid gland; however, when thyroid hormone is taken orally, TG levels tend to be lower than the normal range. In other entities characterized by a low RAIU, such as thyroiditis, leakage of preformed thyroid hormone results in elevated TG levels. If a history of thyroid hormone ingestion is elicited or deduced, exogenous thyroid hormone should be withheld for 4 to 6 weeks, and thyroid function tests should be repeated to ensure a euthyroid state has been restored. Rarely, thyroid hormones may be the drug of abuse and detection is difficult with standard thyroid hormone assays. For example, tiratricol (TRIAC), an endogenous metabolite of T_3 that has been used for weight loss and paradoxically by bodybuilders, will suppress TSH at high doses and may cross-react in many T_3 immunoassays; thus, thyrotoxicosis factitia due to tiratricol abuse may be misinterpreted as T_3 toxicosis, and also lead to serious side effects.

Medications Containing Iodine

Amiodarone may induce thyrotoxicosis (2%–3% of patients), overt hypothyroidism (5% of patients), subclinical hypothyroidism (25% of patients), or euthyroid hyperthyroxinemia, depending on the underlying thyroid function and pathology.[19] Because amiodarone contains 37% iodine by weight, approximately 6 mg/day of iodine is released for each 200 mg of amiodarone, 1,000 times greater than the recommended daily amount of iodine of 150 mcg/day. As a result of this iodine overload, iodine-exacerbated thyroid dysfunction commonly occurs among those patients with preexisting thyroid disease: thyrotoxicosis in patients with hyperthyroidism or euthyroid nodular autonomy and hypothyroidism in patients with autoimmune thyroid disease. In contrast to hyperthyroidism with increased synthesis of thyroid hormone induced by amiodarone (type I), destructive thyroiditis with leakage of TG and thyroid hormones also occurs (type II), typically among individuals with otherwise normal glands. The two types of amiodarone-induced thyrotoxicosis may be differentiated using color-flow Doppler ultrasonography. Such distinction is critically important, given the therapeutic implications of the two syndromes: type I amiodarone-induced hyperthyroidism responds somewhat to thionamides, whereas type II may respond to glucocorticoids.[19] Obviously, RAI therapy is inappropriate in type I due to the drug-induced iodine excess, and in type II due to lack of increased hormone synthesis. The manifestations of amiodarone-induced thyrotoxicosis may be atypical symptoms such as ventricular tachycardia and exacerbation of the underlying chronic obstructive pulmonary disease, both of which are significant, given the severe underlying cardiac pathology that led to the use of amiodarone in the first place. Amiodarone also directly interferes with type I 5'-deiodinase, leading to reduced conversion of T_4 to T_3 and hyperthyroxinemia without thyrotoxicosis.[19]

High intake of biotin can interfere with thyroid hormone assays, leading to false results of thyroid function tests.[20,21] Excess biotin leads to falsely elevated results of TT_4, FT_4, and TT_3 (competitive immunoassays), and to falsely low TSH levels (immunometric or sandwich immunoassays). This is not an issue of endogenous interference but an interference with the assay itself. Biotin doses of greater than 5,000 mcg/day are associated with major interference on immunoassays; in such circumstances, it is recommended patients hold their biotin doses for 24 to 48 hours before laboratory testing.

Thyroid Cancer

In widely metastatic differentiated papillary or follicular carcinomas with relatively well-preserved function, sufficient thyroid hormones can be synthesized and secreted to produce thyrotoxicosis. In most instances, a previous diagnosis of thyroid malignancy has been made. The diagnosis can be confirmed by whole-body ^{131}I scanning. Treatment with ^{131}I is generally effective at ablating functioning thyroid metastases.

Struma Ovarii

Struma ovarii is a teratoma of the ovary that contains differentiated thyroid follicular cells and is capable of making thyroid hormones. This extremely rare cause of thyrotoxicosis is suggested by the absence of thyroid enlargement in a thyrotoxic patient with a suppressed RAIU in the neck and no findings to suggest thyroiditis. The diagnosis is established by localizing functioning thyroid tissue in the ovary with whole-body RAI (sodium iodide-131 [^{131}I]) scanning. Interestingly, struma ovarii not associated with hyperthyroidism is much more common than struma ovarii associated with hyperthyroidism. Because the tissue is neoplastic and potentially malignant, combined surgical and radioiodine treatment of malignant struma ovarii for both monitoring and therapy of relapse is the recommended treatment.

Causes of Thyrotoxicosis Associated with Elevated RAIU

Graves' Disease

1 Graves' disease is an autoimmune syndrome that usually includes hyperthyroidism, diffuse thyroid enlargement, exophthalmos, and, less commonly, pretibial myxedema and thyroid acropachy (Fig. 96-4).[6,9] Graves' disease is the most common cause of hyperthyroidism, with a prevalence estimated to be 3 per 1,000 population in the United States. Hyperthyroidism results from the action of thyroid-stimulating antibodies (TSAbs), which are directed against the thyrotropin receptor on the surface of the thyroid cell. When these immunoglobulins bind to the receptor, they activate downstream G-protein signaling and adenylate cyclase in the same manner as TSH. Autoantibodies that react with orbital muscle and fibroblast tissue in the skin are responsible for the extrathyroidal manifestations of Graves' disease, and these autoantibodies are encoded by the same germline genes that encode for other autoantibodies for striated muscle and thyroid peroxidase. Clinically, the extrathyroidal disorders may not appear at the same

time that hyperthyroidism develops.

FIGURE 96-4

Features of Graves' disease. (*A*) Facial appearance in Graves' disease; lid retraction, periorbital edema, and proptosis are marked. (*B*) Thyroid dermopathy over the lateral aspects of the shins. (*C*) Thyroid acropachy. *(Reproduced with permission from Fauci AS, Kasper DL, Longo DL, et al., eds. Harrison's Principles of Internal Medicine. 16th ed. New York: McGraw Hill; 2005:2114.)*

There is now compelling evidence that heredity predisposes the susceptible individual to the development of clinically overt autoimmune thyroid disease in the setting of appropriate environmental and hormonal triggers. A role for gender in the emergence of Graves' disease is suggested by the fact that hyperthyroidism is approximately eight times more common in women than in men. Other lines of evidence support a role for heredity. First, there is a well-recognized clustering of Graves' disease within some families. Twin studies in Graves' disease have revealed that a monozygotic twin has a 35% likelihood of ultimately developing the disease compared with a 3% likelihood for a dizygotic twin, resulting in an estimation that 79% of the predisposition to Graves' disease is genetic. Second, the occurrence of other autoimmune diseases, including Hashimoto's thyroiditis, is also increased in families of patients with Graves' disease. Third, several studies have demonstrated an increased frequency of certain human leukocyte antigens (HLAs) in patients with Graves' disease. Differing HLA associations have been identified in the various ethnic groups studied. In White patients, for example, the relative risk of Graves' disease in carriers of the HLA-DR3 haplotype is between 2.5 and 5, whereas lesser associations have been reported for HLA-B8 and the HLA-DQA*0501allele. Several gene loci have been associated with autoimmune thyroid diseases such as Graves' disease. It is thought that these susceptibility genes interact with environmental triggers to induce thyroid disease through epigenetic effects.

The thyroid gland is diffusely enlarged in the majority of patients with Graves' disease and is commonly 40 to 60 g (two to three times the normal size). The surface of the gland is either smooth or bosselated, and the consistency varies from soft to firm. For patients with severe disease, a thrill may be felt and a systolic bruit may be heard over the gland, reflecting the increased intraglandular vascularity typical of hyperplasia. Whereas the presence of any of the extrathyroidal manifestations of this syndrome, including exophthalmos, pretibial myxedema, or thyroid acropachy, in a thyrotoxic patient is pathognomonic of Graves' disease, most patients can be diagnosed on the basis of their history and examination of their diffuse goiter (see Fig. 96-4). An important clinical feature of Graves' disease is the occurrence of spontaneous remissions, albeit uncommon. The abnormalities in TSAb production may decrease or disappear over time.

The results of laboratory tests in thyrotoxic Graves' disease include an increase in the overall hormone production rate with a disproportionate increase in T_3 relative to T_4 (Table 96-4). In an occasional patient, the disproportionate overproduction of T_3 is exaggerated, with the result that only the serum T_3 concentration is increased (T_3 toxicosis). The saturation of TBG is increased due to the elevated levels of serum T_4 and T_3. As a result, the concentrations of free T_4 and free T_3 are increased to an even greater extent than are the measured serum total T_4 and T_3 concentrations. The TSH level will be suppressed or undetectable due to negative feedback by elevated levels of thyroid hormone at the pituitary.

TABLE 96-4

Thyroid Function Tests in Different Thyroid Conditions

	Total T_4	Free T_4	Total T_3	TSH
Normal	4.5-10.9 mcg/dL(58-140 nmol/L)	0.8-2.7 ng/dL(10.3-34.7 pmol/L)	60-181 ng/dL(0.92-2.79 nmol/L)	0.5-4.7 mIU/L
Hyperthyroid	↑↑	↑↑	↑↑↑	↓↓[a]
Hypothyroid	↓↓	↓↓	↓	↑↑[a]
Increased TBG	↑	Normal	↑	Normal

[a]Primary thyroid disease.

For the patient with symptomatic disease, measurement of the serum-free T_4 concentration, total T_4, total T_3, and the TSH value will confirm the diagnosis of thyrotoxicosis. For the patient who is not pregnant or lactating, a 24-hour RAIU should be obtained if there is any diagnostic uncertainty, for example, recent onset of symptoms or other factors suggestive of thyroiditis. An increased RAIU indicates that the thyroid gland is inappropriately utilizing the iodine to produce more thyroid hormone at a time when the patient is thyrotoxic.

Thyrotoxic periodic paralysis is a rare complication of hyperthyroidism most commonly observed in Asian and Hispanic populations.[10] It presents as recurrent proximal muscle flaccidity ranging from mild weakness to total paralysis. The paralysis may be asymmetric and usually involves muscle groups that are strenuously exercised before the attack. Cognition and sensory perception are spared, whereas deep tendon reflexes are markedly diminished. The condition is characterized by hypokalemia and low urinary potassium excretion. Hypokalemia results from a sudden shift of potassium from extracellular to intracellular sites rather than reduced total body potassium. High-carbohydrate loads and exercise provoke the attacks. Treatment includes correcting the hyperthyroid state, potassium administration, spironolactone to conserve potassium, and propranolol to minimize intracellular shifts. Some patients with this condition have a mutation in the inwardly rectifying potassium channel Kir2.6.[11]

Toxic Adenoma

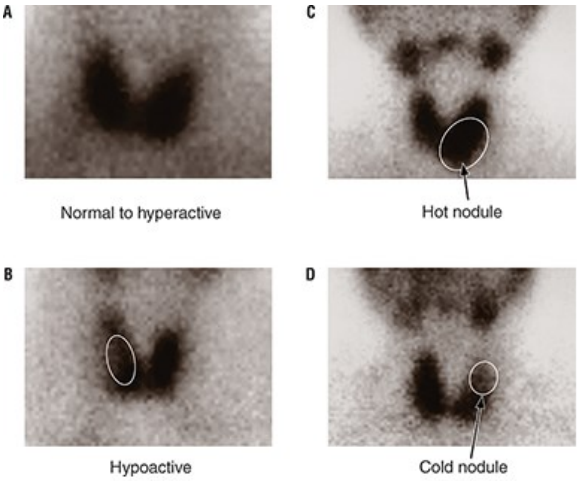
An autonomous thyroid nodule is a discrete thyroid mass whose function is independent of pituitary and TSH control. The prevalence of toxic adenoma ranges from about 2% to 9% of thyrotoxic patients and depends on iodine availability and geographic location. Toxic adenomas are benign tumors that produce thyroid hormones. They arise from gain-of-function somatic mutations of the TSH receptor or, less commonly, the Gsα protein; more than a dozen TSH receptor mutations have been described.[6] These nodules may be referred to as *toxic adenomas*, or "hot" nodules, because of their persistent uptake on a radioiodine thyroid scan, despite suppressed uptake in the surrounding non-nodular gland (Fig. 96-5). The amount of thyroid hormone produced by an autonomous nodule is mass related. Therefore, hyperthyroidism usually occurs with larger nodules (ie, those more than 3 cm in diameter). Older patients (older than 60 years) are more likely (up to 60%) to be thyrotoxic from autonomous nodules than are younger patients (12%). There are many reports of isolated elevation of serum T_3 in patients with autonomously functioning nodules. Therefore, if the T_4 level is normal, a T_3 level must be measured to rule out T_3 toxicosis. If autonomous function is suspected but the TSH is normal, the diagnosis can be confirmed by a failure of the autonomous nodule to decrease its iodine uptake during exogenous T_3 administration sufficient to suppress TSH.

Surgical resection, thionamides, percutaneous ethanol injection, and radioactive iodine (RAI) ablation are treatment options, but since thionamides do not halt the proliferative process in the nodule, definitive therapies are recommended. Ethanol ablation may be associated with pain and damage to surrounding extrathyroidal tissues, limiting its acceptance in the United States. It has been hypothesized that sublethal radiation doses received by the surrounding non-nodular thyroid tissue during RAI therapy of toxic nodules may lead to induction of thyroid cancer. However, thyroid cancer has rarely been associated with RAI therapy, and newer studies suggest hyperthyroidism itself, rather than RAI therapy, as being associated with non-thyroid malignancies.[12] There is a modest positive association between the dose of radioactive iodine absorbed into the gland and risk of solid cancer death;[13] however, the same authors later indicated that after controlling for known confounding, there no longer appeared to be a significant

association in the risk of solid cancer mortality by treatment group.[14] An autonomously functioning nodule, if not large enough to cause thyrotoxicosis, can often be managed conservatively without therapy.

FIGURE 96-5

Radioiodine thyroid scans. (A) Normal or increased thyroid uptake of iodine-125 (^{125}I). (B) Thyroid with a marked decrease in ^{125}I uptake in a large palpable mass. (C) Increased ^{125}I uptake isolated to a single nodule, the "hot nodule." (D) Decreased thyroid ^{125}I uptake in an isolated region, the "cold nodule." *(Reproduced with permission from Molina PE. Endocrine Physiology. 2nd ed. New York: McGraw Hill; 2006:90. Images courtesy of Dr. Luis Linares, Memorial Medical Center, New Orleans, LA.)*



Multinodular Goiters

In multinodular goiters (MNGs), follicles with autonomous function coexist with normal or even nonfunctioning follicles. The pathogenesis of MNG is thought to be similar to that of toxic adenoma: diffuse hyperplasia caused by goitrogenic stimuli, leading to mutations and clonal expansion of benign neoplasms. The functional status of the nodule(s) depends on the nature of the underlying mutations, whether activating such as TSH receptor mutations or inhibitory such as RAS mutations. Thyrotoxicosis in an MNG occurs when a sufficient mass of autonomous follicles generates enough thyroid hormone to exceed the needs of the patient. It is not surprising that this type of hyperthyroidism develops insidiously over a period of several years and predominantly affects older individuals with long-standing goiters. The patient's complaints of weight loss, depression, anxiety, and insomnia may be attributed to old age. Any unexplained chronic illness in an elderly patient presenting with an MNG calls for the exclusion of hidden (silent) thyrotoxicosis.[15] Current third-generation TSH assays are able to detect subclinical hyperthyroidism.

A thyroid scan will show patchy areas of autonomously functioning thyroid tissue intermixed with hypofunctioning areas. When the patient is euthyroid, therapy is based on the need to reduce goiter size due to mass-related symptoms such as dysphagia. Doses of thyroid hormone sufficient to suppress TSH levels may slow goiter growth or cause some degree of shrinkage, but, in general, suppression therapy for nodular disease is inadequate to address mass effect. The preferred treatment for toxic MNG is RAI or surgery. Surgery is usually selected for younger patients and patients in whom large goiters impinge on vital organs. Alternatively, percutaneous injection of 95% ethanol has also been used to destroy single or multinodular adenomas with a 5-year success rate approaching 80%.

Trophoblastic Diseases

Human chorionic gonadotropin (hCG) is a stimulator of the TSH receptor and may cause hyperthyroidism. The basis for the thyrotropic effect of hCG is the structural similarity of hCG to TSH (similar α subunits and unique β subunits). For patients with hyperthyroidism caused by trophoblastic tumors, serum hCG levels usually exceed 300 U/mL (kU/L) and always exceed 100 U/mL (kU/L). The mean peak hCG level in normal pregnancy is 50 U/mL (kU/L). On a molar basis, hCG has only 1/10,000 the activity of pituitary TSH in mouse bioassays. Nevertheless, this thyrotropic activity may be very substantial

for patients with trophoblastic tumors, whose serum hCG concentrations may reach 2,000 U/mL (kU/L).

TSH-Induced Hyperthyroidism

To better understand these syndromes, we must first review TSH biosynthesis and secretion. TSH is synthesized in the anterior pituitary as separate α- and β-subunit precursors. The α subunits from luteinizing hormone (LH), follicle-stimulating hormone (FSH), hCG, and TSH are identical, whereas the β subunits are unique and confer immunologic and biologic specificity. Free β subunits are devoid of receptor-binding and biologic activity and require combination with an α subunit to express their activity. Criteria for the diagnosis of TSH-induced hyperthyroidism include (a) evidence of peripheral hypermetabolism, (b) diffuse thyroid gland enlargement, (c) elevated free thyroid hormone levels, and (d) elevated or inappropriately "normal" serum immunoreactive TSH concentrations. Because the pituitary gland is extremely sensitive to even minimal elevations of free T_4, a "normal" or elevated TSH level in any thyrotoxic patient indicates the inappropriate production of TSH.

TSH-Secreting Pituitary Adenomas

TSH-secreting pituitary tumors occur sporadically and release a biologically active hormone that is unresponsive to normal feedback control.[16] The mean age at diagnosis is around 40 years, with women being diagnosed more than men (8:7). These tumors may co-secrete prolactin or growth hormone; therefore, the patients may present with amenorrhea/galactorrhea or signs of acromegaly. Most patients present with classic symptoms and signs of thyrotoxicosis. Visual field defects may be present due to impingement of the optic chiasm by the tumor. Tumor growth and worsening visual field defects have been reported following antithyroid therapy because lowering of thyroid hormone levels is associated with loss of feedback inhibition from high thyroid hormone levels.

Diagnosis of a TSH-secreting adenoma should be made by demonstrating a lack of TSH response to TRH stimulation, inappropriate TSH levels, elevated α-subunit levels, and radiologic imaging; given the lack of routine availability of TRH, the other three criteria are essential. Note that some small tumors are not identified by MRI. Moreover, 10% of "normal" individuals may have incidental pituitary tumors or other benign focal lesions noted on pituitary imaging.

Transsphenoidal pituitary surgery is the treatment of choice for TSH-secreting adenomas. Pituitary gland irradiation is often given following surgery to prevent tumor recurrence. Dopamine agonists and octreotide have been used to treat tumors, especially those that co-secrete prolactin.

Pituitary Resistance to Thyroid Hormone

Resistance to thyroid hormone is a rare condition that can be due to a number of molecular defects, including mutations in the TRβ gene. Pituitary resistance to thyroid hormone (PRTH) refers to selective resistance of the pituitary thyrotrophs to thyroid hormone. As nonpituitary tissues respond normally to thyroid hormone, patients experience the toxic peripheral effects of thyroid hormone excess. About 90% of patients studied have an appropriate increase in TSH in response to TRH; conversely, the TSH will be suppressed by T_3 administration.

Patients with PRTH require treatment to reduce their elevated thyroid hormone levels. Determining the appropriate serum T_4 level is difficult because TSH cannot be used to evaluate the adequacy of therapy. Any reduction in thyroid hormone carries the risk of inducing thyrotroph hyperplasia. Ideally, agents that suppress TSH secretion could be used to treat these individuals. Glucocorticoids, dopaminergic drugs, somatostatin and its analogs, and thyroid hormone analogs with reduced metabolic activity have all been tried, but with relatively little benefit. β-Blocker therapy can also be used. Triiodothyroacetic acid (TRIAC), an agent that is devoid of thyromimetic properties on peripheral tissues, but blocks the secretion of TSH, has been used to treat this condition. However, it is not available in the United States. Given the ability of retinoid X receptor ligands to inhibit TSH production, drugs such as bexarotene may have therapeutic benefit in PRTH.

CLINICAL PRESENTATION

CLINICAL PRESENTATION: Thyrotoxicosis

General

- Signs and symptoms of thyrotoxicosis affect multiple organ systems. Patients often have symptoms for an extended period before the diagnosis of hyperthyroidism is made.

Symptoms

- The typical clinical manifestations of thyrotoxicosis include nervousness, anxiety, palpitations, emotional lability, easy fatigability, menstrual disturbances, and heat intolerance. A cardinal sign is weight loss despite an increased appetite.
- Elderly patients are more likely to develop atrial fibrillation with thyrotoxicosis than younger patients. The frequency of bowel movements may increase, but frank diarrhea is unusual. For the elderly patient and for the patient with severe disease, anorexia may be present as well. Palpitations are a prominent and distressing symptom, particularly in the patient with preexisting heart disease. Proximal muscle weakness is common and is noted on climbing stairs or in getting up from a sitting position. Women may note their menses are becoming scanty and irregular. Extremely thyrotoxic patients may have tachycardia, heart failure, psychosis, hyperpyrexia, and coma, a presentation described as thyroid storm.[8] Long-term hyperthyroidism may also be associated with a loss of bone mineral density and an increased risk of osteoporosis-related fracture.

Signs

- A variety of physical signs may be observed including warm, smooth, moist skin, exophthalmos (in Graves' disease only), pretibial myxedema (in Graves' disease only), and unusually fine hair. Separation of the end of the fingernails from the nail beds (onycholysis) may be noted. Ocular signs that result from thyrotoxicosis include retraction of the eyelids and lagging of the upper lid behind the globe when the patient looks downward (lid lag). Physical signs of a hyperdynamic circulatory state are common and include tachycardia at rest, a widened pulse pressure, and a systolic ejection murmur. Gynecomastia is sometimes noted in men. Neuromuscular examination often reveals a fine tremor of the protruded tongue and outstretched hands. Deep tendon reflexes are generally hyperactive. Thyromegaly is usually present. Elderly patients may present with the absence of clinical evidence of excess thyroid hormones (palpitations, anxiety, tremor, heat intolerance, and diaphoresis), but instead present with weight loss, apathy, and depression (apathetic hyperthyroidism).

Diagnosis

- Low TSH serum concentration. Elevated free and total T_4 and T_3 serum concentrations, particularly in more severe disease.
- Elevated radioactive iodine uptake (RAIU) by the thyroid gland when the hormone is being overproduced; suppressed RAIU in thyrotoxicosis due to thyroid inflammation (thyroiditis).

Other Tests

- Thyroid-stimulating antibodies (TSAbs)
- TG
- Thyrotropin receptor antibodies

TABLE 96-3

Differential Diagnosis of Thyrotoxicosis Based on Radioactive Iodine Uptake (RAIU)

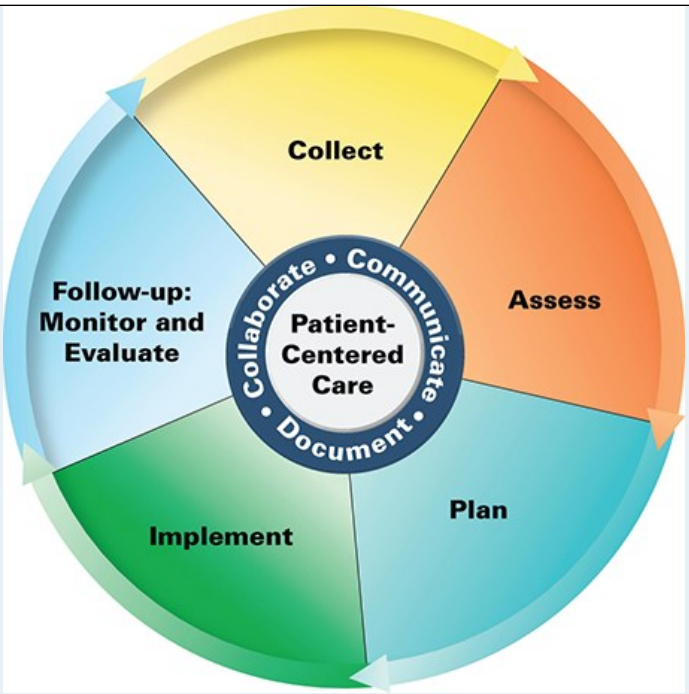
Increased RAIU[a]	Decreased RAIU
TSAb (Graves' disease)	Exogenous sources of thyroid hormone
Multinodular goiter	Medications containing thyroid hormone or iodine
Toxic adenoma	Painless thyroiditis
hCG (trophoblastic diseases)	Subacute thyroiditis
TSH-induced hyperthyroidism	Inflammatory thyroid disease
TSH-secreting tumors	Food sources containing thyroid gland
Selective pituitary resistance to T_4	Ectopic thyroid tissue
Thyroid stimulators other than TSH	Struma ovarii
	Metastatic follicular carcinoma

[a]The RAIU may be decreased if the patient has been recently exposed to excess iodine.

hCG, human chorionic gonadotropin; RAIU, radioactive iodine uptake; TSAb, thyroid-stimulating antibody.

PATIENT CARE PROCESS

Patient Care Process for the Management of Hyperthyroidism



Collect

- Patient characteristics (eg, age, race, sex, pregnancy status)
- Patient history (past medical, family, social) including patient signs and symptoms: warm, smooth, moist skin, palpitations, exophthalmos, pretibial myxedema, and unusually fine hair; anxiety, tremor, heat intolerance, tachycardia, weight loss, and menstrual disturbances (see Clinical Presentation Box)
- Current medications (including over-the-counter [OTC] and herbal medication use)
- Objective data
  - Heart rate, blood pressure (BP), weight, and body mass index (BMI)
  - Labs (eg, FT_4, TT_3, TSH, thyroid-stimulating antibodies; serum electrolytes, Scr, ALT)
  - Other diagnostic tests when indicated (eg, thyroid ultrasound, raidioactive iodine uptake [RAIU] scan)

Assess

- Cause of hyperthyroidism (see Table 96-3)
- Current medications that may contribute to or worsen hyperthyroidism
- Current medications that may interact with antithyroid therapy
- Appropriateness and effectiveness of current antithyroid regimen

Plan*

- Drug therapy regimen including specific antithyroid therapy, dose, and duration (see Table 96-5)
- Monitoring parameters including efficacy (eg, resolution of signs and symptoms) and safety (symptomatic hypothyroidism, adverse effects of medications), laboratory tests (TSH, FT_4, TT_3, LFTs, and CBC), and time frame

- Patient education (eg, purpose of treatment, dietary and lifestyle modification, drug therapy)

Implement*

- Provide patient education regarding all elements of the treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up

Follow-up: Monitor and Evaluate

- Resolution of signs and symptoms
- Presence of adverse effects
- Patient adherence to treatment plan using multiple sources of information

Collaborate with patient, caregivers, and other healthcare professionals.

TREATMENT

Thyrotoxicosis

2 Three common treatment modalities are used in the management of hyperthyroidism: surgery, antithyroid medications, and RAI (Table 96-5).

TABLE 96-5

Treatments for Hyperthyroidism Caused by Graves' Disease

Treatment	Advantages	Disadvantages	Comment
• Methimazole (first-line pharmacotherapy) • Propylthiouracil (second-line pharmacotherapy)	• Noninvasive • Low initial cost • Low risk of permanent hypothyroidism • Possible remissions due to immune effects	• Low cure rate (average 40%-50%) • Adverse drug reactions • Drug compliance	• First-line treatment in children, adolescents, and pregnancy • Initial treatment in severe cases or preoperative preparation
Radioactive iodine (^{131}I)	• Cure of hyperthyroidism • Lowest cost, before adjustment for quality of life	• Permanent hypothyroidism almost inevitable • Might worsen ophthalmopathy • Pregnancy must be deferred for 6-12 months; no breast-feeding • Small potential risk of exacerbation of hyperthyroidism	Best treatment for toxic nodules and toxic multinodular goiter
Surgery	Rapid, effective treatment, especially in patients with large goiters	• Most invasive • Least costly in long term after quality-of-life adjustment • Permanent hypothyroidism • Pain, scar	• Potential choice in pregnancy (2nd trimester) if major side effect from ATDs • Potential complications (recurrent laryngeal nerve damage, hypoparathyroidism) • Useful when coexisting suspicious nodule present • Option for patients who refuse radioiodine

Desired Outcomes

The overall therapeutic objectives are to eliminate the excess thyroid hormone and minimize the symptoms and long-term consequences of hyperthyroidism.

General Approach to Treatment

Therapy must be individualized based on the type and severity of hyperthyroidism, patient age and gender, the existence of nonthyroidal conditions, and response to previous therapy.[22,23] For example, patients with swallowing or breathing difficulties due to impingement of the esophagus or trachea are generally taken for surgical removal of the thyroid. Clinical guidelines for the treatment of hyperthyroidism have been published.[6] Selected recommendations from these guidelines are shown in Table 96-6.

TABLE 96-6

Selected Recommendations from the American Thyroid Association Hyperthyroidism Guidelines

Question	Recommendation Strength	Quality of Evidence
How should thyrotoxicosis be evaluated and initially managed?	β-Adrenergic blockade is recommended in all patients with symptomatic thyrotoxicosis, especially elderly patients and thyrotoxic patients with resting heart rates in excess of 90 beats per minute or coexistent cardiovascular disease.	Strong recommendation, moderate quality
If ^{131}I therapy is chosen (*for GD*), how should it be accomplished?	Sufficient radiation should be administered in a single dose (typically 10-15 mCi [370-555 MBq]) to render the patient with GD hypothyroid.	Strong recommendation, moderate quality
If ATDs are chosen as initial management of GD, how should the therapy be managed?	Methimazole should be used in virtually every patient who chooses antithyroid drug therapy for GD, except during the first trimester of pregnancy when propylthiouracil is preferred, in the treatment of thyroid storm, and in patients with minor reactions to methimazole who refuse radioactive iodine therapy or surgery.	Strong recommendation, moderate quality
If ATDs are chosen as initial management of GD, how should patients be monitored?	A differential WBC count should be obtained during febrile illness and at the onset of pharyngitis in all patients taking antithyroid medication.	Strong recommendation, low-quality
If thyroidectomy is chosen for treatment of GD, how should it be accomplished?	If surgery is chosen as the primary therapy for GD, near-total or total thyroidectomy is the procedure of choice.	Strong recommendation, low quality
If thyroidectomy is chosen for treatment of GD, how should it be accomplished?	Patients should be rendered euthyroid prior to the procedure.	Strong recommendation, moderate quality
How should overt hyperthyroidism due to TMNG or TA be managed?	Patients should be treated with RAI therapy or thyroidectomy.	Weak recommendation, moderate quality
How should GD	Children with GD should be treated with MMI, RAI therapy, or thyroidectomy. RAI therapy should be avoided in	Strong

be managed in children and adolescents?	very young children (<5 years). Under age 5, thyroidectomy should be performed.	recommendation, moderate quality
How should hyperthyroidism in pregnancy be managed?	ATD therapy should be used for overt hyperthyroidism due to GD during pregnancy. PTU should be used when ATD therapy is given during the first trimester. MMI should be used when ATD therapy is started after the first trimester.	Strong recommendation, low quality
How should antithyroid treatment be managed during pregnancy?	GD during pregnancy should be treated with the lowest possible dose of ATDs needed to keep the mother's thyroid hormone levels at or slightly above the reference range for total T_4 and T_3 values in pregnancy (1.5 times above nonpregnant reference ranges in the second and third trimesters), and the TSH below the reference range for pregnancy. Similarly, free T_4 levels should be kept at or slightly above the upper limit of the pregnancy trimester reference range for the assay. Thyroid function should be assessed monthly, and the ATD dose adjusted as required.	Strong recommendation, low quality
How should other causes of thyrotoxicosis be managed?	Patients taking medications known to cause thyrotoxicosis, including interferon (IFN)-α, interleukin-2, tyrosine kinase inhibitors, and lithium, should be monitored clinically and biochemically at 6-month intervals for the development of thyroid dysfunction.	Strong recommendation, low quality

GD, Graves' disease; ^{131}I, radioactive I-131; TMNG, toxic multinodular goiter; TA, toxic adenoma; SH, subclinical hyperthyroidism.

Data from Reference [6].

Nonpharmacologic Therapy

Surgery should be considered for patients with a large thyroid gland (more than 80 g), severe ophthalmopathy, and a lack of remission on antithyroid drug treatment. In case of cosmetic issues or pressure symptoms, the choice in MNG stands between surgery, which is still the first choice, and radioiodine therapy if uptake is adequate. In addition to surgery, the solitary nodule, whether hot or cold, can be treated with percutaneous ethanol injection therapy. For hot nodules, radioiodine is the therapy of choice.[6] Appropriate preparation of the patient for thyroidectomy includes MMI until the patient is biochemically euthyroid (usually 6-8 weeks), followed by the addition of iodides (500 mg/day) for 10 to 14 days before surgery to decrease the vascularity of the gland. Propranolol for several weeks preoperatively and 7 to 10 days after surgery has also been used to maintain a pulse rate of less than 90 beats/min. Combined pretreatment with propranolol and 10 to 14 days of potassium iodide has also been advocated.

The overall complication rate when surgery is performed for MNG by an experienced endocrine surgeon is low. If subtotal thyroidectomy, or an operation that attempts to maintain euthyroidism, is performed for Graves' disease, there is a risk of recurrence of hyperthyroidism that is directly related to remnant thyroid gland size. Near-total thyroidectomy is generally recognized as the procedure of choice for patients with Graves' disease.[6] The complication rates of surgery for Graves' disease are low when surgery is performed by a high-volume thyroid surgeon. Surgical complications include hypoparathyroidism (up to 2%) and laryngeal nerve injury (up to 1%).

Pharmacologic Therapy

Antithyroid Medications

Thionamide Drugs

Two drugs within this category, MMI and PTU, are approved for the treatment of hyperthyroidism in the United States.[23] They are classified as thioureylenes (thionamides), which incorporate an N–C–S=N group into their ring structures.

Mechanism of Action

MMI and PTU share several mechanisms to inhibit the biosynthesis of thyroid hormone.[24] These drugs serve as preferential substrates for the iodinating intermediate of thyroid peroxidase and divert iodine away from potential iodination sites in TG. This prevents subsequent incorporation of iodine into iodotyrosines and ultimately iodothyronine ("organification"). Second, they inhibit the coupling of MIT and DIT to form T_4 and T_3. The coupling reaction may be more sensitive to these drugs than the iodination reaction. Experimentally, these drugs exhibit immunosuppressive effects, although the clinical relevance of this finding is unclear. For patients with Graves' disease, antithyroid drug treatment has been associated with lower TSAb titers and restoration of normal suppressor T-cell function. However, perchlorate (ClO_4^-), which has a different mechanism of action, also decreases TSAbs, suggesting that normalization of the thyroid hormone level may itself improve the abnormal immune function. PTU inhibits the peripheral conversion of T_4 to T_3. This effect is dose-related and occurs within hours of PTU administration. MMI does not have this effect. After several weeks of use, depletion of stored hormone and lack of continuing synthesis of thyroid hormone results in the clinical effects of these drugs.

Pharmacokinetics

Both ATDs are well absorbed (80%-95%) from the gastrointestinal tract, with peak serum concentrations about 1 hour after ingestion. The plasma half-life ranges of PTU and MMI are 1 to 2.5 and 6 to 9 hours, respectively, and are not appreciably affected by thyroid status. Urinary excretion is about 35% for PTU and less than 10% for MMI. These drugs are actively concentrated in the thyroid gland, which may account for the disparity between their relatively short plasma half-lives and the effectiveness of once-daily dosing regimens even with PTU. Approximately 60% to 80% of PTU is bound to plasma albumin, whereas MMI is not protein-bound. MMI readily crosses the placenta and appears in breast milk. Older studies suggested that PTU crosses the placental membranes only one-tenth as well as MMI; however, these studies were done in the course of therapeutic abortion early in pregnancy. Newer studies show little difference between fetal concentrations of PTU and MMI, and both are associated with elevated TSH in about 20% and low T_4 in about 7% of fetuses.

Dosing and Administration

MMI is available as 5 and 10 mg tablets and PTU as 50 mg tablets. MMI is approximately 10 to 20 times more potent than PTU. Initial therapy with MMI is given in two or three divided doses totaling 30 to 60 mg/day. PTU is given in dose ranges from 300 to 600 mg daily, usually in three or four divided doses. Although the traditional recommendation is for divided doses, evidence exists that both drugs can be given as single daily doses. Patients with severe hyperthyroidism may require larger initial doses, and some may respond better at these larger doses if the dose is divided. The maximal blocking doses of MMI and PTU are 120 and 1,200 mg daily, respectively. Once the intrathyroidal pool of thyroid hormone is reduced and new hormone synthesis is sufficiently blocked, clinical improvement should ensue. Usually, within 4 to 8 weeks of initiating therapy, symptoms will diminish and circulating thyroid hormone levels will return to normal. Now, the tapering regimen can be started. Changes in dose for each drug should be made monthly because the endogenously produced T_4 will reach a new steady-state concentration in this interval. Typical ranges of daily maintenance doses for MMI and PTU are 5 to 30 mg and 50 to 300 mg, respectively.

If the objective of therapy is to induce long-term remission in a patient with Graves' Disease, the patient should remain on continuous antithyroid drug therapy for a minimum of 12 to 24 months. Antithyroid drug therapy induces permanent remission rates of 10% to 98%, with an overall average of about 40% to 50%. This is much higher than the remission rate seen with propranolol alone (22%–36%). Patient characteristics for a favorable outcome include older patients (older than 40 years), low T_4:T_3 ratio (less than 20), a small goiter (less than 50 g), short duration of disease (less than 6 months), no previous history of relapse with ATDs, duration of therapy 1 to 2 years or longer, and low TSAb titers at baseline or a reduction with treatment.[24] A 2012 study provides preliminary evidence that a new assay that has better specificity for detection of antibodies that stimulate the TSH receptors, without detecting coexistent blocking antibodies, may be a useful predictor of remission of Graves' disease.[25]

A remission of Graves' hyperthyroidism most often occurs after 4 to 11 years of treatment, with a better prognosis if TSH binding inhibitor immunoglobulin (TBII) activity disappeared within 5 years without TBII fluctuation or enlargement of the goiter. A longer duration until normalization of TBII and higher final thyroid weight were associated with a poor prognosis.[26]

In another study in which patients were treated for their first episodes of Graves' hyperthyroidism, patients were treated for a minimum of 18 to 24

months of methimazole and then randomized to receive an additional 36 to 102 months of treatment or discontinued methimazole. Patients in both treatment groups were followed 48 months after discontinuing methimazole. Patients who received 60 to 120 months of methimazole were significantly more likely to achieve remission compared to patients who received only an 18- to 24-month course of treatment (85% vs 47%).[27]

A systematic review on remission rates in children with Graves' disease found that 23.7% of the participants achieved remission after 1.5 to 2.5 years of treatment and 75% achieved remission after 9 years of treatment. Adverse events occurred in 17.6% of patients but major side effects occurred in only 1.1%. In summary, longer treatment was associated with greater efficacy and is generally well tolerated.[28]

It is important that patients be followed every 6 to 12 months after remission occurs. If a relapse occurs, alternate therapy with RAI is preferred over a second course of ATDs, however, continued long-term low-dose MMI can be considered.[29] Relapses seem to plateau after about 5 years and eventually, 5% to 20% of patients will develop spontaneous hypothyroidism. Some researchers have speculated whether concurrent administration of T_4 with thionamide therapy for thyrotoxicosis and subclinical hyperthyroidism can reduce autoantibodies directed toward the thyroid gland and improve the remission rate. In general, this approach is not recommended because of the higher rates of side effects seen with the larger doses of ATDs needed for this regimen.[6]

Subclinical hyperthyroidism is defined as a serum TSH below the lower limit of the reference range combined with free T_4 and T_3 concentrations that are normal. Subclinical hyperthyroidism is associated with an increased risk of atrial fibrillation and may be associated with increased all-cause mortality. Some studies show an increased risk of hip fractures in postmenopausal women with subclinical hyperthyroidism. Most practitioners agree that the treatment of older patients (greater than 65 years) with TSH values below 0.1 mIU/L is reasonable. In patients who are younger or have TSH values of 0.1 to 0.4 mIU/L a decision whether to treat the patient for mild hyperthyroidism or to monitor thyroid function depends on the patient's cardiovascular risk factors and bone health.[6,30]

Adverse Effects

Minor adverse reactions to MMI and PTU have an overall incidence of 5% to 25% depending on the dose and the drug, whereas major adverse effects occur in 1.5% to 4.6% of patients receiving these drugs.[23] Pruritic maculopapular rashes (sometimes associated with vasculitis based on skin biopsy), arthralgias, and fevers occur in up to 5% of patients and may occur at a greater frequency with higher doses and in children. Rashes often disappear spontaneously but, if persistent, may be managed with antihistamines. Under the supervision of an allergist, desensitization to methimazole is an option for treating patients who experience rash or itching from the drug.[31]

One of the most common side effects is a benign transient leukopenia characterized by a WBC count of less than 4,000/mm^3 (4×10^9/L) This condition occurs in up to 12% of adults and 25% of children and sometimes can be confused with mild leukopenia seen in Graves' disease. This mild leukopenia is not a harbinger of the more serious adverse effect of agranulocytosis, so therapy can usually be continued. If a minor adverse reaction occurs with one ATD, the alternate thiourea may be tried, but cross-sensitivity occurs for about 50% of patients.[23]

Agranulocytosis is one of the serious adverse effects of thiourea drug therapy and is characterized by fever, malaise, gingivitis, oropharyngeal infection, and a granulocyte count less than 250/mm^3 (0.250×10^9/L).[23] These drugs are concentrated in granulocytes, and this reaction may represent a direct toxic effect rather than hypersensitivity. This toxic reaction has occurred with both thioureas, and the incidence varies from 0.5% to 6%. It is higher for patients over age 40 receiving an MMI dose greater than 40 mg/day or the equivalent dose of PTU, and is more frequent with initial MMI doses of 30 mg compared with 15 mg. A systematic review and meta-analysis found strong associations of ATD-induced agranulocytosis with HLAB* 27:05, HLA-B*38:02, and HLA-DRB1*08:03 alleles, especially in carbimazole/methimazole-induced agranulocytosis.[32]

Agranulocytosis usually develops in the first 3 months of therapy. Because the onset is sudden, routine WBC count monitoring has not been recommended. Colony-stimulating factors have been used with some success to restore cell counts to normal, but it is unclear how effective this form of therapy is compared with routine supportive care. Peripheral lymphocytes obtained from patients with PTU-induced agranulocytosis undergo a transformation in the presence of other thionamides, suggesting that these severe reactions are immunologically mediated and patients should not receive other thionamides. Aplastic anemia has been reported with MMI and may be associated with an inhibitor to colony-forming units. Once ATDs are discontinued, clinical improvement is seen over several days to weeks. Patients should be counseled to discontinue therapy and contact their physician when flu-like symptoms such as fever, malaise, or a sore throat develops. Treatment of agranulocytosis requires immediate suspension of

the ATD and initiation of broad-spectrum antibiotics. Definitive treatment of hyperthyroidism is subsequently required.[33] Clinicians will often concomitantly provide an order for a complete blood cell count (with WBC count differential) when prescribing MMI or PTU therapy. If the patient becomes ill and is unable to reach the provider, the patient can still visit the nearest laboratory to have potential agranulocytosis diagnosed.

Arthralgias and a lupus-like syndrome (sometimes in the absence of antinuclear antibodies) have been reported in 4% to 5% of patients. This generally occurs after 6 months of therapy. Uncommonly, polymyositis, presenting as proximal muscle weakness and elevated creatine phosphokinase, has been reported with PTU administration. Gastrointestinal intolerance is also reported to occur in 4% to 5% of patients. Hypoprothrombinemia is a rare complication of thionamide therapy. Patients who have experienced a major adverse reaction to one thiourea drug should not be converted to the alternate drug because of cross-sensitivity.[6]

In 2019 the European Medicines Agency (EMA) issued a warning and the product labeling for methimazole was changed to include acute pancreatitis as a serious side effect. This decision was based on six case reports of acute pancreatitis in patients treated with methimazole, developing within 90 days of starting the drug. In one study, ongoing use of methimazole was associated with a 56% increase in the risk of being admitted to the hospital for acute pancreatitis, whereas propylthiouracil was not associated with an increased risk.[34]

Hepatotoxicity can be seen with both MMI and PTU, with a prevalence of approximately 1.3%. At moderate doses, some authors have found that initial hepatic enzyme elevations eventually normalize in most patients with continued therapy. PTU-induced subclinical liver injury is common and is usually transient and asymptomatic. Thus, it has generally been thought that therapy with PTU may be continued with caution in the absence of symptoms and hyperbilirubinemia. However, a 1997 literature review documented 49 cases of hepatotoxicity. Twenty-eight cases were associated with PTU use, and 21 cases were associated with MMI use. The hepatotoxicity was associated with seven deaths and three deaths in the PTU and MMI groups, respectively. There did not appear to be a relationship between the dose or duration of thionamide treatment and outcome. During the past 20 years of PTU use in the United States, 22 adults developed severe hepatotoxicity leading to nine deaths and five liver transplants. The risk of this complication was greater in children (1:2,000) than in adults (1:10,000). A recent reanalysis of data reported to the Food and Drug Administration (FDA) from 1982 to 2008 found that toxicity in children was generally related to higher doses of PTU and that toxicity in both children and adults was associated with therapy lasting more than 4 months in duration.[35] Thus, the American Thyroid Association (ATA) and the FDA recommend against the use of PTU as first-line therapy in either adults or children.[6] One of three exceptions includes the first trimester of pregnancy, when the risk of MMI-induced embryopathy may exceed that of PTU-induced hepatotoxicity. Other exceptions include intolerance to MMI and thyroid storm.

Older reports suggested that congenital skin defects (ie, aplasia cutis) may be caused by MMI and carbimazole, although a registry review from the Netherlands could not find an association between maternal use of these drugs and skin defects. Several serious congenital malformations including tracheoesophageal fistulas and choanal atresia have been observed with MMI and carbimazole but not PTU use during pregnancy. PTU has traditionally been considered the drug of choice throughout pregnancy for women with hyperthyroidism, because of concerns about the possible teratogenic effects of MMI. However, currently heightened concerns about the greater risk of hepatotoxicity with PTU when compared to MMI have led to the recommendation that PTU no longer be considered a first-line drug, except during the first trimester of pregnancy. The choice of antithyroid agent during pregnancy has been further complicated by two studies that suggest that fetuses exposed to either MMI or PTU during gestation may increase the risk of drug-induced fetal malformations. A Danish study revealed that 2% to 3% of children exposed to PTU developed birth defects associated with this therapy.[36] In another study, PTU-associated birth defects, though less severe than MMI-associated birth defects, occurred with similar incidence in a Korean population.[37] Recommendations regarding the management of thyroid disease during pregnancy recommends using the lowest effective dose of the ATD as possible, targeting maternal serum FT_4/TT_4 at the upper limit or moderately above the reference range and utilizing a team approach with close collaboration among endocrinologists, maternal-fetal medicine specialists, and neonatologists.[38]

While there is debate regarding optimal therapy of Graves' disease, a study assessing the quality of life (QoL) in patients 6 to 10 years after treatment for Graves' disease with RAI, thyroidectomy, or ATDs. Patients treated with RAI had worse thyroid-related and general QoL than patients treated with ATD or thyroidectomy on the majority of QoL scales. However, regardless of treatment modality, patients with GD had worse thyroid-related QoL 6 to 10 years after diagnosis compared to the general population.[39]

Iodides

Iodide was the first form of drug therapy for Graves' disease. Its mechanism of action is to acutely block thyroid hormone release, inhibit thyroid hormone biosynthesis by interfering with intrathyroidal iodide utilization (the Wolff–Chaikoff effect), and decrease the size and vascularity of the

gland. This early inhibitory effect provides symptom improvement within 2 to 7 days of initiating therapy, and serum T_4 and T_3 concentrations may be reduced for a few weeks. Despite the reduced release of T_4 and T_3, thyroid hormone synthesis continues at an accelerated rate, resulting in a gland rich in stored hormones. The normal and hyperfunctioning thyroid soon escapes from this inhibitory effect within 1 to 2 weeks by decreasing the active transfer of iodide into the gland. Iodides are often used as adjunctive therapy to prepare a patient with Graves' disease for surgery, to acutely inhibit thyroid hormone release and quickly attain the euthyroid state in severely thyrotoxic patients with cardiac decompensation, or to inhibit thyroid hormone release following RAI therapy. However, large doses of iodine may exacerbate hyperthyroidism or indeed precipitate hyperthyroidism in some previously euthyroid individuals (Jod–Basedow disease). This Jod–Basedow phenomenon is most common in iodine-deficient areas, particularly for patients with pre-existing nontoxic goiter. Iodide is contraindicated in toxic MNG as the autonomous tissue utilizes the iodine for subsequent thyroid hormone synthesis. Although it is not the standard of care in the United States, potassium iodide therapy was effective in two-thirds of cases, and induced remission in approximately 40% of the patients in a Japanese study of hyperthyroid patients with thionamide-associated side effects.[40] Because iodide crosses the placenta and may cause hypothyroidism and goiter in the newborn, its use is generally avoided in pregnant women.

Potassium iodide is available either as a saturated solution (SSKI), which contains 38 mg of iodide per drop or as Lugol's solution, which contains 6.3 mg of iodide per drop. The typical starting dose of SSKI is 3 to 10 drops daily (120-400 mg) in water or juice. There is no documented advantage to using doses in excess of 6 to 8 mg/day. When used to prepare a patient for surgery, it should be administered 7 to 14 days preoperatively. As an adjunct to RAI, SSKI should not be used before, but rather 3 to 7 days after RAI treatment, so that the radioactive iodide can concentrate in the thyroid. The most frequent toxic effects with iodide therapy are hypersensitivity reactions (skin rashes, drug fever, rhinitis, and conjunctivitis), salivary gland swelling, "iodism" (metallic taste, burning mouth and throat, sore teeth and gums, symptoms of a head cold, and sometimes stomach upset and diarrhea), and gynecomastia.

Other compounds containing organic iodide have also been used therapeutically for hyperthyroidism. These include various radiologic contrast media that share a triiodoaminobenzene and monoaminobenzene ring with a propionic acid chain (eg, iopanoic acid and sodium ipodate). The effect of these compounds is a result of the iodine content inhibiting thyroid hormone release as well as competitive inhibition of 5'- monodeiodinase conversion related to their structures, which resemble thyroid analogs. Unfortunately, these extremely useful agents are no longer available in the United States.

Adrenergic Blockers

Because many of the manifestations of hyperthyroidism are mediated by β-adrenergic receptors, β-blockers (especially propranolol) have been used widely to ameliorate symptoms such as palpitations, anxiety, tremor, and heat intolerance. Although β-blockers are quite effective for symptom control, they have no effect on the urinary excretion of calcium, phosphorus, hydroxyproline, creatinine, or various amino acids, suggesting a lack of effect on peripheral thyrotoxicosis and protein metabolism. Furthermore, β-blockers neither reduce TSAb nor prevent thyroid storm. Propranolol and nadolol partially block the conversion of T_4 to T_3, but this contribution to the overall therapeutic effect is small in magnitude. Inhibition of conversion of T_4 to T_3 is mediated by D-propranolol, which is devoid of β-blocking activity, and L-propranolol, which is responsible for the antiadrenergic effects, has little effect on the conversion.

β-Blockers are usually used as adjunctive therapy with ATDs, RAI, or iodides when treating Graves' disease or toxic nodules; in preparation for surgery; or in thyroid storm. The only conditions for which β-blockers are primary therapy for thyrotoxicosis are those associated with thyroiditis. The dose of propranolol required to relieve adrenergic symptoms is variable, but an initial dose of 20 to 40 mg four times daily is effective (goal heart rate less than 90 beats/min) for most patients. Younger or more severely toxic patients may require as much as 240 to 480 mg/day because there seems to be an increased clearance rate for these patients. β-Blockers are contraindicated for patients with decompensated heart failure unless it is caused solely by tachycardia (high output failure). Nonselective agents and those lacking intrinsic sympathomimetic activity should be used with caution for patients with asthma and bronchospastic chronic obstructive lung disease. β-Blockers that are cardioselective and have intrinsic sympathomimetic activity may have a slight margin of safety in these situations. Other patients in whom contraindications exist are those with sinus bradycardia, those receiving monoamine oxidase inhibitors or tricyclic antidepressants, and those with spontaneous hypoglycemia. β-Blockers may also prolong gestation and labor during pregnancy. Other side effects include nausea, vomiting, anxiety, insomnia, light-headedness, bradycardia, and hematologic disturbances.

Antiadrenergic agents such as centrally acting sympatholytics and calcium channel antagonists may have some role in the symptomatic treatment of

hyperthyroidism. These drugs might be useful when contraindications to β-blockade exist. When compared with nadolol 40 mg twice daily, clonidine 150 mcg twice daily reduced plasma catecholamines, whereas nadolol increased both epinephrine and norepinephrine after 1 week of treatment. Diltiazem 120 mg given every 8 hours reduced heart rate by 17%; fewer ventricular extrasystoles were noted after 10 days of therapy, and diltiazem has been shown to be comparable to propranolol in lowering heart rate and BP.

Therapeutic plasmapheresis is an effective alternative treatment option to prepare for ablative treatment in patients that have side effects or who do not respond adequately to anti-thyroid drugs.[41] In a retrospective study in patients with Graves' disease, amiodarone-induced thyrotoxicosis, or toxic nodular goiter, the median free triiodothyronine (FT_3) fell from 9.9 pg/mL to 4.0 pg/mL (0.15 pmol/L to 0.06 pmol/L) and FT_4 levels fell from 2.9 ng/dL to 1.6 ng/dL (37.3 pmol/L to 20.6 pmol/L). Each apheresis session lasted for 2.5 to 3 hours and was performed daily until normal thyroid function was achieved (median 4, range 1-7 days).

Radioactive Iodine

Although other radioisotopes have been used to ablate thyroid tissue, ^{131}I is considered to be the agent of choice for Graves' disease, toxic autonomous nodules, and toxic MNGs.[6] RAI is administered as a colorless and tasteless liquid that is well absorbed and concentrates in the thyroid. ^{131}I is a β- and γ-emitter with a tissue penetration of 2 mm and a half-life of 8 days. Other organs take up ^{131}I, but the thyroid gland is the only organ in which organification of the absorbed iodine takes place. Initially, RAI disrupts hormone synthesis by incorporating into thyroid hormones and TG. Over a period of weeks, follicles that have taken up RAI and surrounding follicles develop evidence of cellular necrosis, breakdown of follicles, development of bizarre cell forms, nuclear pyknosis, and destruction of small vessels within the gland, leading to edema and fibrosis of the interstitial tissue. Pregnancy is an absolute contraindication to the use of RAI since radiation will be delivered to the fetal tissue, including the fetal thyroid.

β-Blockers may be given any time without compromising RAI therapy, accounting for their role as a mainstay of adjunctive therapy to RAI treatment. If iodides are administered, they should be given 3 to 7 days after RAI to prevent interference with the uptake of RAI in the thyroid gland. Because thyroid hormone levels will transiently increase following RAI treatment due to the release of preformed thyroid hormone, patients with cardiac disease and elderly patients are often treated with thionamides prior to RAI ablation. For patients with underlying cardiac disease, it may be necessary to reinstitute antithyroid drug therapy following RAI ablation. The standard practice is to withdraw the thionamide 4 to 6 days prior to RAI treatment and to reinstitute it 4 days after therapy is concluded. Administering antithyroid drug therapy immediately following RAI treatment may result in a higher rate of posttreatment recurrence or persistent hyperthyroidism. Pretreatment with PTU may lead to higher rates of treatment failure, but this does not appear to be the case with MMI pretreatment. The use of lithium, as adjunctive therapy to RAI therapy, has multiple benefits of increasing the cure rate, shortening the time to cure, and preventing a post-therapy increase in thyroid hormone levels.[42] Lithium is likely to achieve these effects by increasing RAI retention in the thyroid and inhibiting thyroid hormone release from the gland, although it is not commonly used due to its narrow therapeutic index.

Corticosteroid administration will blunt and delay the rise in antibodies to the TSH receptor, TG, and thyroid peroxidase while reducing T_3 and T_4 concentrations following RAI. Theoretically, if a shared thyroidal and orbital antigen is involved in the pathogenesis of Graves' ophthalmopathy, antigen released with RAI treatment could aggravate pre-existing eye disease. There is some disagreement as to what degree of ophthalmopathy should be considered a contraindication to RAI. However, in those with moderate or severe orbitopathy, it seems reasonable to delay RAI until the patient's eye disease has been stable. Traditionally, corticosteroids, radiation therapy, and surgical correction have been the mainstays of therapy for Graves' ophthalmopathy. Rituximab, tocilizumab, and teprotumumabIn have been assessed in RCTs.[43] In 2020, the FDA approved teprotumumab, a monoclonal anti-insulin-like growth factor I receptor antibody for the treatment of thyroid eye disease. Patients completing the eight-infusion treatment course of teprotumumab over 24 weeks demonstrated significant improvement in proptosis, diplopia, quality of life, and Clinical Activity Score.[44] The most commonly reported adverse events with teprotumumab were muscle spasm (18%), hearing loss (10%), and hyperglycemia (8%).

Destruction of the gland attenuates the hyperthyroid state, and hypothyroidism commonly occurs months to years following RAI.[6,24] The goal of therapy is to destroy overactive thyroid cells, and a single dose of 4,000 to 8,000 rad (40 to 80 Gy) results in a euthyroid state in 60% of patients at 6 months or less. The remaining 40% become euthyroid within 1 year, requiring two or more doses. It is advisable that a second dose of RAI be given 6 months after the first RAI treatment if the patient remains hyperthyroid.[6] Variables that predict an unsuccessful outcome of RAI include gender (men are less likely to develop hypothyroidism), race, the size of the thyroid (euthyroidism is less likely in large glands), the severity of disease, and perhaps a higher level of TSAb. Predictors of successful treatment with RAI included higher ablative dose, female gender, lower free T_4 levels at diagnosis, and

absence of a palpable goiter.[24] The acute, short-term side effects of ^{131}I therapy are minimal and include mild thyroidal tenderness and dysphagia. Concern about mutations and congenital defects now appears to be unfounded because long-term follow-up studies have not revealed an increased risk for these complications.[45] Although RAI is very effective in the treatment of hyperthyroidism, long-term follow-up from Great Britain suggests that among patients with hyperthyroidism treated with RAI, mortality from all causes and mortality resulting from cardiovascular and cerebrovascular disease and fracture are increased.

A common approach to Graves' hyperthyroidism is to administer a single dose of 5 to 15 mCi (185 to 555 mBq; 80-200 μCi/g of tissue [3.0 to 7.4 mBq/g]). The optimal method for determining ^{131}I treatment doses for Graves' hyperthyroidism is unknown, and techniques have varied from a fixed dose to more elaborate calculations based on gland size, iodine uptake, and iodine turnover.[6] In a trial of 88 patients with Graves' disease, no difference in outcome was seen among high or low, fixed or adjusted doses. Thyroid glands estimated to weigh more than 80 g may require larger doses of RAI. Larger doses are likely to induce hypothyroidism and are seldom given outside the United States due to the imposition of stringent safety restrictions. For example, in the United Kingdom, a nursery school teacher is advised to stay out of school for 3 weeks following a 15 mCi (555 mBq) dose of ^{131}I.

Special Populations

Graves' Disease and Pregnancy

Inappropriate increase in the production of hCG is a cause of abnormal thyroid function tests during the first half of pregnancy, and hCG can cause either subclinical (normal T_4 and suppressed TSH) or overt hyperthyroidism. This is because the homology of hCG and TSH leads to hCG-mediated stimulation through the TSH receptor. At hCG concentrations greater than 400 IU/mL (kIU/L), TSH levels were invariably suppressed and free T_4 levels were generally above the normal range. Most patients with hCG greater than 200 IU/mL (kIU/L) did not have symptoms of hyperthyroidism. The variability of the thyrotropic potency of hCG is believed to depend on its carbohydrate composition.

A very comprehensive guideline has been published by the ATA regarding the management of thyroid disease during pregnancy.[38] Hyperthyroidism during pregnancy is almost solely caused by Graves' disease, with approximately 0.1% to 0.4% of pregnancies affected. Although the increased metabolic rate is usually well tolerated in pregnant women, two symptoms suggestive of hyperthyroidism during pregnancy are failure to gain weight despite a good appetite and persistent tachycardia. There is no increase in maternal mortality or morbidity in well-controlled patients. However, postpartum thyroid storm has been reported in about 20% of untreated individuals. Fetal loss is also more common, due to the fact that spontaneous abortion and premature delivery are more common in untreated pregnant women, as are low-birth-weight infants and eclampsia. Transplacental passage of TSAb may occur, causing fetal as well as neonatal hyperthyroidism. An uncommon cause of hyperthyroidism is molar pregnancy; women present with a large-for-dates uterus and evacuation of the uterus is the preferred management approach.

Because RAI is contraindicated in pregnancy and surgery is usually not recommended (especially during the first trimester), antithyroid drug therapy is usually the treatment of choice for hyperthyroidism. MMI readily crosses the placenta and appears in breast milk.

As previously mentioned, propylthiouracil has been considered the drug of choice during the first trimester of pregnancy, with the lowest possible doses used to maintain the maternal T_4 level in the high-normal range.[38] During this period the risk of MMI-associated embryopathy is believed to outweigh that of PTU-associated hepatotoxicity. To prevent fetal goiter and suppression of fetal thyroid function, PTU is usually prescribed in daily doses of 300 mg or less and tapered to 50 to 150 mg daily after 4 to 6 weeks. PTU doses of less than 200 mg daily are unlikely to produce fetal goiter. During the second and third trimesters, when the critical period of organogenesis is complete, MMI has been thought to be the drug of choice because of the greater risk of hepatotoxicity with PTU.[38] However, it is unclear whether this strategy of switching thionamides, and thus exposing the fetus to both drugs, is the optimum approach.[36] Thionamide doses should be adjusted to maintain free T_4 within 10% of the upper normal limit of the nonpregnant reference range. During the last trimester, TSAbs fall spontaneously, and some patients will go into remission so that ATD doses may be reduced. A rebound in maternal hyperthyroidism occurs in about 10% of women postpartum and may require more intensive treatment than in the last trimester of pregnancy.

Neonatal and Pediatric Hyperthyroidism

Following delivery, some babies of hyperthyroid mothers will be hyperthyroid due to placental transfer of TSAbs, which stimulates thyroid hormone

production in utero and postpartum. This is likely if the maternal TSAb titers were quite high. The disease is usually expressed 7 to 10 days postpartum and treatment with ATDs (PTU 5-10 mg/kg/day or MMI 0.5-1 mg/kg/day) may be needed for as long as 8 to 12 weeks until the antibody is cleared (immunoglobulin G half-life is about 2 weeks). Iodide (potassium iodide one drop per day or Lugol's solution one to three drops per day) and sodium ipodate may be used for the first few days to acutely inhibit hormone release.

Childhood hyperthyroidism has classically been managed with either MMI or PTU. Long-term follow-up studies suggest that this form of therapy is quite acceptable, with 25% of a cohort experiencing remission every 2 years. Again, current recommendations suggest using MMI as a first-line agent in both adults and children.[6]

Thyroid Storm

Thyroid storm is a life-threatening medical emergency characterized by decompensated thyrotoxicosis, high fever (often more than 39.4°C [103°F]), tachycardia, tachypnea, dehydration, delirium, coma, nausea, vomiting, and diarrhea.[8] Graves' disease and less commonly toxic nodular goiter are usually the underlying thyrotoxic pathology.

Precipitating factors for thyroid storm include infection, trauma, surgery, RAI treatment, and withdrawal from ATDs. Although the duration of clinical decompensation lasts for an average duration of 72 hours, symptoms may persist up to 8 days. With aggressive treatment, the mortality rate has been lowered to 20%. The following therapeutic measures should be instituted promptly: (a) suppression of thyroid hormone formation and secretion, (b) antiadrenergic therapy, (c) administration of corticosteroids, and (d) treatment of associated complications or coexisting factors that may have precipitated the storm. Specific agents used in thyroid storm are outlined in Table 96-7. PTU in large doses may be the preferred thionamide because, in addition to interfering with the production of thyroid hormones, it also blocks the peripheral conversion of T_4 to T_3. However, β-blockers and corticosteroids will serve the same purpose. A theoretical advantage of MMI is that it has a longer duration of action. If patients are unable to take medications orally, the tablets can be crushed into suspension and instilled by a gastric or rectal tube. Iodides, which rapidly block the release of preformed thyroid hormone, should be administered after thionamide is initiated to inhibit iodide utilization by the overactive gland. If iodide is administered first, it could theoretically provide a substrate to produce even higher levels of thyroid hormone.

TABLE 96-7

Drug Dosages Used in the Management of Thyroid Storm

Drug	Regimen
Propylthiouracil	900-1,200 mg/day orally in four or six divided doses
Methimazole	90-120 mg/day orally in four or six divided doses
Sodium iodide	Up to 2 g/day IV in single or divided doses
Lugol's solution	5-10 drops three times a day in water or juice
Saturated solution of potassium iodide (SSKI)	1-2 drops three times a day in water or juice
Propranolol	40-80 mg every 6 hours
Dexamethasone	5-20 mg/day orally or IV in divided doses
Prednisone	25-100 mg/day orally in divided doses
Methylprednisolone	20-80 mg/day IV in divided doses
Hydrocortisone	100-400 mg/day IV in divided doses

Antiadrenergic therapy with the short-acting agent esmolol is preferred, both because it may be used in the patient with pulmonary disease or at risk for cardiac failure and because its effects may be rapidly reversed. Corticosteroids are generally recommended, although there is no convincing evidence of adrenocortical insufficiency in thyroid storm, and the benefits derived from steroids may be caused by their antipyretic action and their effect of stabilizing BP.[8] General supportive measures, including acetaminophen as an antipyretic (do not use aspirin or other NSAIDs because they may displace bound thyroid hormone), fluid and electrolyte replacement, sedatives, digitalis, antiarrhythmics, insulin, and antibiotics, should be given as indicated. Plasmapheresis and peritoneal dialysis have been used to remove excess hormone (and to remove thyroid-stimulating immunoglobulins in Graves' disease) when the patient has not responded to more conservative measures, although these measures do not always work.

EVALUATION OF THERAPEUTIC OUTCOMES—THYROTOXICOSIS

After therapy (surgery, thionamides, or RAI) for hyperthyroidism has been initiated, patients should be evaluated on a monthly basis until they reach a euthyroid condition. Clinical signs of continuing thyrotoxicosis (tachycardia, weight loss, and heat intolerance, among others) or the development of hypothyroidism (bradycardia, weight gain, and lethargy, among others) should be noted. β-Blockers may be used to control symptoms of thyrotoxicosis until the definitive treatment has returned the patient to a euthyroid state. If T_4 replacement is initiated, the goal is to maintain both the free T_4 level and the TSH concentration in the normal range. Once a stable dose of T_4 is identified, the patient may be followed up every 6 to 12 months.

A common, potentially confusing clinical situation should be mentioned. Some patients may have TSH concentrations that continue to be suppressed despite having free T_4 concentrations that become normal or low. For patients with long-standing hyperthyroidism, the pituitary thyrotrophs are responsible for making TSH become atrophic. The average amount of time required for these cells to resume normal functioning is 6 to 8 weeks. Therefore, if a thyrotoxic patient has his or her free T_4 concentration lowered rapidly before the thyrotrophs resume normal function, a period of "transient central hypothyroidism" will be observed. In addition, autoimmune mechanisms may also play a role, with a slower TSH recovery in patients with higher titers of thyroid-binding inhibitory immunoglobulins.

CONCLUSION—HYPERTHYROIDISM

Management of hyperthyroidism includes treatment with ATDs, RAI, or thyroidectomy. Optimal treatment is patient-specific, depending on patient clinical presentation, including age, history of arrhythmias or atherosclerotic disease, goiter size, and severity of thyrotoxicosis. ATDs are the primary therapy during pregnancy.

HYPOTHYROIDISM

Hypothyroidism is defined as the clinical and biochemical syndrome resulting from decreased thyroid hormone production.[46] Biochemically, primary hypothyroidism is defined as TSH concentrations above the reference range and FT_4 and/or triiodothyronine levels below the reference range.

EPIDEMIOLOGY—HYPOTHYROIDISM

Overt hypothyroidism occurs in 1.5% to 2% of women and 0.2% of men, and its incidence increases with age. In the Third National Health and Nutrition Examination Survey (NHANES III), levels of serum TSH and total T_4 were measured in a representative sample of adolescents and adults (age 12 or older). Among 16,533 people who neither were taking thyroid medication nor reported histories of thyroid disease, 3.9% had subclinical hypothyroidism (serum TSH more than 4.5 mIU/L, and T_4 normal), and 0.2% had “clinically significant” hypothyroidism (TSH more than 4.5 mIU/L, and T_4 less than 4.5 mcg/dL [58 nmol/L]).[7] Subclinical hypothyroidism is commonly regarded as a sign of impending thyroid failure.

ETIOLOGY AND PATHOPHYSIOLOGY —HYPOTHYROIDISM

The vast majority of patients have primary hypothyroidism due to thyroid gland failure caused by chronic autoimmune thyroiditis. Special populations with higher risk of developing hypothyroidism include postpartum women, individuals with a family history of autoimmune thyroid disorders and patients with previous head and neck or thyroid irradiation or surgery, other autoimmune endocrine conditions (eg, type 1 diabetes mellitus, adrenal insufficiency, and ovarian failure), some other nonendocrine autoimmune disorders (eg, celiac disease, vitiligo, pernicious anemia, Sjögren’s syndrome, and multiple sclerosis), primary pulmonary hypertension, and Down’s and Turner’s syndromes.

Central hypothyroidism is rare and affects both sexes equally. It is more often associated with pituitary than hypothalamic disorders but frequently involves both.[47] Biochemically, central hypothyroidism is defined by low or low-to-normal TSH concentrations and a disproportionately low concentration of FT_4. Secondary hypothyroidism due to pituitary failure is uncommon but should be suspected in a patient with decreased levels of T_4 and inappropriately normal or low TSH levels. Most patients with secondary hypothyroidism due to inadequate TSH production will have clinical signs of more generalized pituitary insufficiency, such as abnormal menses and decreased libido, or evidence of a pituitary adenoma, such as visual field defects, galactorrhea, or acromegaloid features, but isolated TSH deficiency can be congenital or acquired as a result of autoimmune hypophysitis.[48] Generalized (peripheral and central) resistance to thyroid hormone is extremely rare.

Table 96-8 outlines the causes of hypothyroidism. These causes fall into two broad categories involving dysfunction of the thyroid gland (primary hypothyroidism) or dysfunction of the pituitary or hypothalamus (secondary hypothyroidism).

TABLE 96-8

Causes of Hypothyroidism

- **Primary hypothyroidism**
- Hashimoto's disease
- Iatrogenic hypothyroidism
- Less common:
  - Iodine deficiency
  - Enzyme defects
  - Thyroid hypoplasia
  - Goitrogens

- **Secondary hypothyroidism**
- Pituitary disease
- Hypothalamic disease

Chronic Autoimmune Thyroiditis

Autoimmune thyroiditis (Hashimoto's disease) is the most common cause of spontaneous hypothyroidism in the adult.[46] Patients may present either with goitrous thyroid gland enlargement and mild hypothyroidism or with thyroid gland atrophy and more severe thyroid hormone deficiency. Both forms of autoimmune thyroiditis probably result from cell- and antibody-mediated thyroid injury. The presence of specific defects in suppressor T-lymphocyte function leads to the survival of a randomly mutating clone of helper T lymphocytes, which are directed against normally occurring antigens on the thyroid membrane. Once these T lymphocytes interact with thyroid membrane antigen, B lymphocytes are stimulated to produce thyroid antibodies. Readers are referred to an excellent review regarding biochemical testing in thyroid disorders.[49] Antithyroid peroxidase (antimicrosomal) antibodies are present in virtually all patients with Hashimoto's thyroiditis and appear to be directed against the enzyme thyroid peroxidase. These antibodies are capable of fixing complement and inducing cytotoxic changes in thyroid cells. Antibodies that are capable of stimulating thyroid growth through interaction with the TSH receptor may occasionally be found particularly in goitrous hypothyroidism; conversely, antibodies that inhibit the trophic effects of TSH may be present in the atrophic type.

Iatrogenic Hypothyroidism

Iatrogenic hypothyroidism follows exposure to destructive amounts of radiation (radioiodine or external radiation) or surgery. Hypothyroidism occurs within 3 months to a year after ^{131}I therapy in most patients treated for Graves' disease. Thereafter, it occurs at a rate of approximately 2.5% each year. External radiation therapy to the region of the thyroid using doses of greater than 2,500 centigray (cGy) for therapy of neck carcinoma also causes hypothyroidism. This effect is dose-dependent and more than 50% of patients who receive more than 4,000 cGy to the thyroid bed develop hypothyroidism. Total thyroidectomy causes hypothyroidism within 1 month. Excessive doses of thionamides used to treat hyperthyroidism can also cause iatrogenic hypothyroidism.

Other Causes of Primary Hypothyroidism

Iodine deficiency, enzymatic defects within the thyroid gland, thyroid hypoplasia, and maternal ingestion of goitrogens during fetal development may cause cretinism. Early recognition and treatment of the resultant thyroid hormone deficiency is essential for optimal mental development. Large-scale neonatal screening programs in North America, Europe, Japan, and Australia are now in place. The frequency of congenital hypothyroidism in North America and Europe is 1 per 3,500 to 4,000 live births. In the United States, there are racial differences in the incidence of congenital hypothyroidism, with White patients being affected seven times as frequently as Black patients.

In the adult, hypothyroidism is rarely caused by iodine deficiency and goitrogens. Iodine ingestion in the form of expectorants can lead to

hypothyroidism. In sensitive persons (particularly those with autoimmune thyroiditis), the iodide blocks the synthesis of thyroid hormone, leading to increased secretion of TSH and thyroid enlargement. Thus, both iodine excess and iodine deficiency can cause decreased secretion of thyroid hormone. An example of a goitrogen that can induce hypothyroidism is raw bok choy. Several medications can cause hypothyroidism, including lithium, amiodarone, interferon-α, interleukin-2, tyrosine kinase inhibitors, perchlorate, and checkpoint inhibitors.[50]

Pituitary Disease

TSH is required for normal thyroid secretion. Thyroid atrophy and decreased thyroid secretion follow pituitary failure. Pituitary insufficiency may be caused by the destruction of thyrotrophs by either functioning or nonfunctioning pituitary tumors, surgical therapy, external pituitary radiation, postpartum pituitary necrosis (Sheehan's syndrome), trauma, and infiltrative processes of the pituitary such as metastatic tumors, tuberculosis, histiocytosis, and autoimmune mechanisms.[51] In all these situations, TSH deficiency most often occurs in association with other pituitary hormone deficiencies. The identification of secondary hypothyroidism due to bexarotene use has led to a recognition of the role of rexinoids and retinoids to cause dysregulation of TSH production.[52]

Note that pituitary enlargement in hypothyroidism does not invariably indicate the presence of a primary pituitary tumor. Pituitary enlargement is seen in patients with severe primary hypothyroidism due to compensatory hyperplasia and hypertrophy of the thyrotrophs. With thyroid hormone replacement therapy, serum TSH concentrations decline, indicating that the TSH secretion is not autonomous, and the pituitary resumes a more normal configuration. These patients are easily separated from patients with primary pituitary failure by measuring a TSH level.

Hypothalamic Disease

TRH deficiency also causes a rare form of secondary hypothyroidism (also referred to as tertiary hypothyroidism). In both adults and children, it may occur from cranial irradiation, trauma, infiltrative diseases, or neoplastic diseases.

CLINICAL PRESENTATION

CLINICAL PRESENTATION: Hypothyroidism

General

- Hypothyroidism can lead to a variety of end-organ effects with a wide range of disease severity, from entirely asymptomatic to coma with multisystem failure. In the adult, manifestations of hypothyroidism are nonspecific. In the child, thyroid hormone deficiency may manifest as delays in growth or intellectual development.
- Thyroid hormone is essential for normal growth and development during embryonic life. Uncorrected thyroid hormone deficiency during fetal and neonatal development results in mental retardation and/or cretinism. Both in children and adults, there is a slowing of physical and mental activity, as well as of cardiovascular, gastrointestinal, and neuromuscular function.

Symptoms

- Common symptoms of hypothyroidism include dry skin, cold intolerance, weight gain, constipation, and weakness.
- Complaints of lethargy, depression, fatigue, exercise intolerance, or loss of ambition and energy are also common but are less specific.
- Muscle cramps, myalgia, and stiffness are frequent complaints of hypothyroid patients.
- Menorrhagia and infertility may present commonly in women.

Signs

- Objective weakness is common, with proximal muscles being affected more than distal muscles. Slow relaxation of deep tendon reflexes is common.
- The most common signs of decreased levels of thyroid hormone include coarse skin and hair, cold or dry skin, periorbital puffiness, and bradycardia.
- Speech is often slow, and the voice may be hoarse.
- Reversible neurologic syndromes such as carpal tunnel syndrome, polyneuropathy, and cerebellar dysfunction may also occur.
- Galactorrhea may be found in women.

Diagnosis

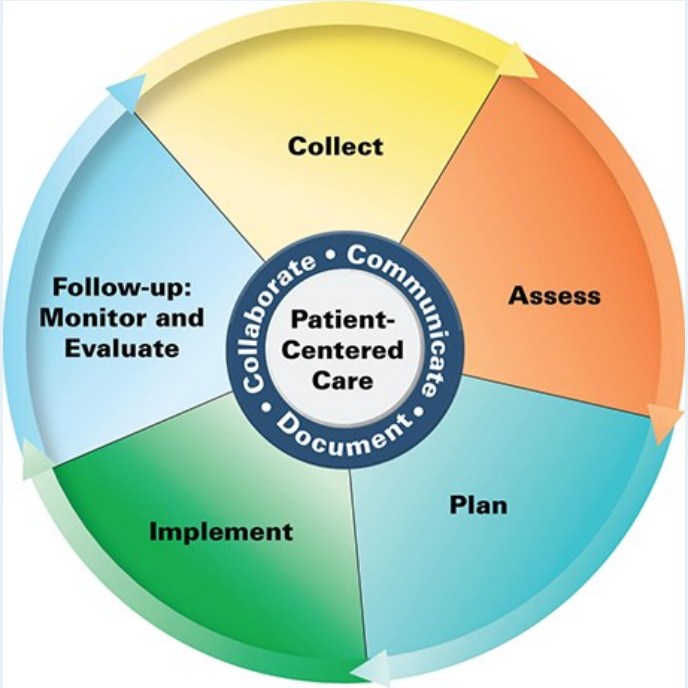
- A rise in the TSH is the first evidence of hypothyroidism in primary hypothyroidism.
- In secondary hypothyroidism in patients with pituitary disease, serum TSH concentrations are generally low or normal. A serum TSH concentration in the normal range is clearly inappropriate if the patient's T_4 is low.
- Many patients will have a free T_4 level within the normal range (compensated or subclinical hypothyroidism), with few, if any, symptoms of hypothyroidism. As the disease progresses, the free T_4 concentration will drop below the normal level. With increased TSH stimulation, thyroidal production will shift toward greater amounts of T_3, and thus T_3 concentrations will often be maintained in the normal range in spite of a low T4. Eventually, free and/or total T_4 and T_3 serum concentrations should be low.

Other Tests

- TPOAbs and anti-TG antibodies are likely to be elevated in autoimmune thyroiditis.

PATIENT CARE PROCESS

Patient Care Process for the Management of Hypothyroidism



Collect

- Patient characteristics (eg, age, race, sex, pregnancy status)
- Patient history (past medical, family, social) including signs and symptoms: coarse skin and hair, cold or dry skin, periorbital puffiness, and bradycardia; cold intolerance, weight gain, constipation, weakness, muscle cramps, myalgia, and galactorrhea (see Clinical Presentation Box)
- Current medications (including OTC and herbal medication use)
- Objective data
  - Heart rate, BP, weight, and BMI
  - Labs (eg, TSH, FT_4, TT_3, anti-TG antibodies, TPO antibodies; serum electrolytes, Scr, ALT)
  - Other diagnostic tests when indicated (eg, thyroid ultrasound, RAIU scan)

Assess

- Cause of hypothyroidism (see Table 96-8)
- Current medications that may contribute to or worsen hypothyroidism
- Current medications that may interact with thyroid hormone replacement therapy
- Appropriateness and effectiveness of current thyroid hormone replacement regimen

Plan*

- Drug therapy regimen including specific thyroid hormone replacement therapy and dose (see Table 96-9)
- Monitoring parameters including efficacy (eg, resolution of signs and symptoms) and safety (arrhythmias, angina, osteoporosis, or symptomatic hyperthyroidism), laboratory data (TSH, FT_4, TT_3), and follow-up monitoring time frame
- Patient education (eg, purpose of treatment, dietary and lifestyle modification, drug therapy)

Implement*

- Provide patient education regarding all elements of the treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up visits and laboratory tests

Follow-up: Monitor and Evaluate

- Resolution of signs and symptoms
- Presence of adverse effects
- Patient adherence to treatment plan using multiple sources of information

Collaborate with patient, caregivers, and other healthcare professionals.

TREATMENT

Hypothyroidism

Most cases of hypothyroidism result from progressive and permanent damage to the thyroid gland. Replacement of thyroid hormone is the cornerstone of treatment.

Desired Outcomes

The goals of therapy are to restore normal thyroid hormone concentrations in tissue, provide symptomatic relief, prevent neurologic deficits in newborns and children, and reverse the biochemical abnormalities of hypothyroidism.

General Approach to Treatment

Levothyroxine (L-thyroxine, T_4) is considered to be the drug of choice for treatment of hypothyroidism (Table 96-9).[18] Other commercially available thyroid preparations can be obtained but are not considered preferred therapy. Available thyroid preparations are synthetic (L-thyroxine, liothyronine, and liotrix) or natural in origin (ie, desiccated thyroid). The preparations containing both T_4 and T_3 (liotrix, desiccated thyroid) have relatively high proportions of T_3 and may cause thyrotoxicosis.[18] Liothyronine is a short-acting preparation that requires dosing multiple times a day in order to achieve stable hormone concentrations. The availability of sensitive and specific assays for total and free hormone levels as well as TSH now allows precise dose titration to make adequate replacement without inadvertent overdose. The response of TSH to TRH had been advocated for use by some in order to “fine tune” thyroid replacement, but this is not necessary if the third-generation chemiluminometric assays for TSH, which have detection limits of about 0.01 mIU/L, are used. Clinical guidelines for the management of hypothyroidism have been published by the ATA and provide specific treatment recommendations and critically examine the use of combination therapy with T_4 and T_3[18] (Table 96-10).

TABLE 96-9

Thyroid Preparations Used in the Treatment of Hypothyroidism

Drug (Brand Name)	Dosage Form	Content	Relative Dose	Comments/Equivalency
• Thyroid USP • (Armour Thyroid, Nature-Throid, Westhroid, WP Thyroid) T_4:T_3 ratio approximately 4.2:1	Doses include 1/4, 1/2, 1, 2, 3, 4, and 5 grain tabletsArmour 1 grain = 60 mg; Nature-Throid and Westhroid, 1 grain = 65 mg.	Desiccated pork thyroid gland	1 grain (equivalent to 74 mcg of T_4)	High T_3:T_4 ratio; inexpensive
• Levothyroxine • (Euthyrox, Levoxyl, Synthroid,Unithroid,Tirosint, and Tirosint-SOL)	25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, 300 mcg tablets Tirosint 13-150 mcg liquid in gelatin capsule Liquid solution: 13, 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, and 200 mcg in unit-dose ampules injection: 200 and 500 mcg per vial	Synthetic T_4	100 mcg	Stable; predictable potency; generics may be bioequivalent; when switching from natural thyroid to L-thyroxine, lower dose by one-half grain; variable absorption between products; half-life = 7 days, so daily dosing; considered to be drug of choice
• Liothyronine • (Cytomel)	5, 25, and 50 mcg tablets	Synthetic T_3	33 mcg (~equivalent to 100 mcg T_4)	Uniform absorption, rapid onset; half-life = 1.5 days, rapid peak and troughs
• Liotrix • (Thyrolar)	1/4-, 1/2-, 1-, 2-, and 3-grain tablets	Synthetic T_4:T_3 in 4:1 ratio	Thyrolar 1 = 50 mcg T_4 and 12.5 mcg T_3 (~equivalent to 100 mcg T_4)	Stable; predictable; expensive; risk of T_3 thyrotoxicosis because of high ratio of T_3 relative to T_4

TABLE 96-10

Selected Recommendations from the American Thyroid Association Hypothyroidism Guidelines

Question	Synopsis or Paraphrase of Recommendation	Grading
Is levothyroxine monotherapy considered to be the standard of care for hypothyroidism?	Levothyroxine is recommended as the preparation of choice for the treatment of hypothyroidism due to its efficacy in resolving the symptoms of hypothyroidism.	Strong recommendation, moderate quality
What are the clinical and biochemical goals for	Levothyroxine replacement therapy has three main goals. These are (i) to	Strong

levothyroxine replacement in primary hypothyroidism?	provide resolution of the patients' symptoms and hypothyroid signs, (ii) to achieve normalization of serum thyrotropin, and (iii) to avoid overtreatment.	recommendation, moderate quality
Are there situations in which therapy with levothyroxine dissolved in glycerin and supplied in gelatin capsules may have advantages over standard levothyroxine?	Although there are preliminary small studies suggesting that levothyroxine dissolved in glycerin and supplied in gelatin capsules may be better absorbed than standard levothyroxine, the present lack of controlled long-term outcome studies does not support a recommendation for the use of such preparations in these circumstances.	Weak recommendation, low quality
What factors determine the levothyroxine dose required by a hypothyroid patient for reaching the appropriate serum thyrotropin goal?	When deciding on a starting dose of levothyroxine, the patient's weight, lean body mass, pregnancy status, etiology of hypothyroidism, degree of thyrotropin elevation, age, and general clinical context should all be considered.	Strong recommendation, moderate quality
What is the best approach to initiating and adjusting levothyroxine therapy?	Thyroid hormone therapy should be initiated as an initial full replacement or as a partial replacement with gradual increments in the dose titrated upward using serum thyrotropin as the goal. Dose adjustments should be made, with thyrotropin assessment 4-6 weeks after any dosage change.	Strong recommendation, moderate quality
What approach should be taken in patients treated for hypothyroidism who have normal serum thyrotropin values but still have unresolved symptoms?	A minority of patients with hypothyroidism, but normal serum thyrotropin values, may perceive a suboptimal health status of unclear etiology. Acknowledgment of the patients' symptoms and evaluation for alternative causes is recommended in such cases.	Weak recommendation, low quality
In adults requiring thyroid hormone replacement treatment for primary hypothyroidism, is treatment with thyroid extracts superior to treatment with levothyroxine alone?	We recommend that levothyroxine be considered as routine care for patients with primary hypothyroidism, in preference to use of thyroid extracts. High-quality controlled long-term outcome data are lacking to document the superiority of this treatment compared to levothyroxine therapy.	Strong recommendation, moderate quality
In adults requiring thyroid hormone replacement treatment for primary hypothyroidism, is combination treatment including levothyroxine and liothyronine superior to the use of levothyroxine alone?	There is no consistently strong evidence of superiority of combination therapy over monotherapy with levothyroxine. Therefore, we recommend against the routine use of combination treatment with levothyroxine and liothyronine as a form of thyroid replacement therapy in patients with primary hypothyroidism.	Weak recommendation, moderate quality
In adults requiring thyroid hormone replacement treatment for primary hypothyroidism who feel unwell while taking levothyroxine, is combination treatment including levothyroxine and liothyronine superior to the use of levothyroxine alone?	For patients with primary hypothyroidism who feel unwell on levothyroxine therapy alone, there is currently insufficient evidence to support the routine use of a trial of a combination of levothyroxine and liothyronine therapy outside a formal clinical trial or N-of-1 trial, due to uncertainty in the long-term risk-benefit ratio of the treatment.	Insufficient evidence
Are there data regarding therapy with triiodothyronine alone, either as standard liothyronine or as sustained release triiodothyronine, that support the use of triiodothyronine therapy alone for the treatment of hypothyroidism?	Although short-term outcome data in hypothyroid patients suggest that thrice-daily synthetic liothyronine may be associated with beneficial effects on parameters such as weight and lipids, longer-term controlled clinical trials are needed before considering synthetic liothyronine therapy for routine clinical use.	Strong recommendation, moderate quality

Data from Reference [10].

Strong recommendation: Benefits clearly outweigh risks and burden, or risks and burden clearly outweigh benefits. Weak recommendation: Benefits finely balanced with risks and burden. Quality of evidence: High, moderate, or low.

Pharmacologic Therapy

Levothyroxine is the drug of choice for thyroid replacement and suppressive therapy because it is chemically stable, relatively inexpensive, active when orally administered, free of antigenicity, and has uniform potency. Levothyroxine (T_4) administration results in a pool of thyroid hormones that is readily converted to T_3 when needed; in this regard, levothyroxine may be thought of as a prohormone.

Liothyronine (T_3) is chemically pure with a known potency and has a shorter half-life of 1.5 days. Although it can be used diagnostically in the T_3 suppression test, T_3 has some clinical disadvantages, including a higher incidence of cardiac adverse effects, higher cost, and difficulty in monitoring with conventional laboratory tests. If used, T_3 needs to be administered three times a day and it may take a prolonged period of adjustment to achieve stable euthyroidism. Liotrix is a combination of synthetic T_4 and T_3 in a 4:1 ratio. It is chemically stable and pure and has a predictable potency. The major limitations to this product are high cost and lack of therapeutic rationale because most T_3 is peripherally converted from T_4. In addition, the T_4:T_3 ratio is much higher than the 14:1 molar ratio produced by the thyroid gland in humans.

9 The use of combination therapy of levothyroxine and liothyronine remains highly controversial with conflicting results from clinical trials.[53] The American Thyroid Association, British Thyroid Association, and European Thyroid Association reviewed the latest basic science and clinical evidence regarding thyroid hormone combination therapy and published a position statement to guide the design of future clinical trials of T_4/T_3 therapy.[54] A well-designed, adequately powered clinical trial of combination therapy in patients dissatisfied with levothyroxine replacement therapy is anticipated.

A study conducted in rats suggested impairment of type 2 deiodinase activity in the whole body during levothyroxine monotherapy due to deiodinase inactivation, compared with maintenance of deiodinase activity in the hypothalamus.[55] The lesser activation in the hypothalamus leads to efficient T_3 production in the hypothalamus and normalization of TSH before T_3 is normalized in the rest of the body. Accompanying the inactivation of type 2 deiodinase in other tissues, lower serum T_3 and higher T_4/T_3 ratios were seen in rats during monotherapy with L-thyroxine, compared with combination therapy employing a subcutaneous slow-release T_3 pellet. Clinical trials of a slow-release T_3 preparation, other than a pharmacokinetic study of T_3 sulfate in profoundly hypothyroid individuals,[56] has yet to be conducted.

Desiccated thyroid has historically been derived from pig, beef, or sheep thyroid glands, although pigs are currently the usual source. The United States Pharmacopeia requires thyroid USP to contain 38 mcg (±15%) of L-thyroxine and 9 mcg (±10%) of liothyronine for each 60 to 65 mg (one grain). Thyroid USP, as an animal protein-derived product, may be antigenic in allergic or sensitive patients. Even though desiccated thyroid is inexpensive, its limitations preclude it from being considered as a drug of choice for hypothyroid patients.

Pharmacokinetics

The half-life of levothyroxine is approximately 7 days. This long half-life is responsible for a stable pool of prohormone and the need for only once-daily dosing with levothyroxine. Older studies with levothyroxine suggested that bioavailability was low and erratic; however, this product has been reformulated, and the average bioavailability improved to approximately 80%. Different levothyroxine preparations contain different excipients such as dyes and fillers. However, because the relationship between T_4 concentration and TSH is not linear, very small changes in T_4 concentration can lead to substantial changes in TSH, which is a more accurate reflection of hormone replacement status. The FDA mandates that L-thyroxine bioequivalency testing be done using normal volunteers (600 mcg in the fasted state) and three baseline free T_4 concentrations be used to correct for endogenous T_4 production. Bioequivalency is based on the area under the curve (AUC) and maximum concentration (C_{max}) of T_4 out to 48 hours. Approximately 70% of the AUC is derived from endogenous production. TSH is not considered, and it is now very clear that T_4 is too insensitive as a measure of bioequivalency.[57] To avoid overtreatment and undertreatment, once a product is selected, switches between levothyroxine products in patients who

are stable are not recommended. Several levothyroxine products are available, including AB1, AB2, AB3, and AB4 rated products. This has created several permutations for product interchangeability since no reference drug is mandated in bioequivalency testing.

Adverse Effects

Serious untoward effects are unusual if dosing is appropriate and the patient is carefully monitored during the initial treatment. Suboptimal thyroid hormone therapy including under-replacement and over-replacement is common among patients with hypothyroidism.[58] Levothyroxine replacement in athyreotic hypothyroid patients restores systolic and diastolic left ventricular performance within 2 weeks, and the use of levothyroxine may increase the frequency of atrial premature beats but not necessarily ventricular premature beats. Excessive doses of thyroid hormone may lead to heart failure, atrial fibrillation, angina pectoris, and myocardial infarction; rarely, the latter may be caused by coronary artery spasm. Allergic or idiosyncratic reactions can occur with natural animal-derived products such as desiccated thyroid, but these are extremely rare with the synthetic products used today. The 0.05 mg (50 mcg) Synthroid tablet is the least allergenic (due to a lack of dye and few excipients) and should be tried for the patient suspected to be allergic to thyroid hormone tablets.

Hyper-remodeling of cortical and trabecular bone due to hyperthyroidism leads to reduced bone density and may increase the risk of fracture. Compared with normal controls, excess exogenous thyroid hormone results in histomorphometric and biochemical changes similar to those observed in osteoporosis and untreated hyperthyroidism.[59] The risk for this complication seems to be related to the dose of levothyroxine, patient age, and gender. Markers for bone turnover include urinary *N*-telopeptides, pyridinoline crosslinks of type I collagen, osteocalcin, procollagen type 1 N-terminal propeptide, and bone-specific alkaline phosphatase. When doses of levothyroxine are used to suppress TSH concentrations to below-normal values (eg, less than 0.3 mIU/L) in postmenopausal women, this adverse effect is more likely to be seen. Cortical bone is affected to a greater degree than trabecular bone at suppressive doses of L-thyroxine. In contrast, it appears to be much less likely in men and in premenopausal women. Maintaining the TSH between 0.7 and 1.5 mIU/L does not alter bone mineral density in premenopausal women. Although not all studies have shown consistent results, a cohort study suggests that treatment with L-thyroxine to achieve a normal TSH has no adverse effect on bone density.[60]

Drug-Drug and Drug-Food Interactions

The time to maximal absorption of levothyroxine is about 2 hours and this should be considered when T_4 concentrations are determined. Ingestion of L-thyroxine with food can impair its absorption.[18] This can potentially affect the TSH concentration achieved if levothyroxine timing with respect to food is varied. Mucosal diseases, such as celiac sprue, diabetic diarrhea, and ileal bypass surgery, can also reduce absorption. Cholestyramine, calcium carbonate, sucralfate, aluminum hydroxide, ferrous sulfate, soybean formula, dietary fiber supplements, and espresso coffee may also impair the absorption of levothyroxine from the gastrointestinal tract (reviewed extensively in recent hypothyroidism guidelines[18]). Acid suppression with histamine blockers and proton pump inhibitors may also reduce levothyroxine absorption. Drugs that increase nondeiodinative T_4 clearance include rifampin, carbamazepine, and possibly phenytoin. Selenium deficiency and amiodarone may block the conversion of T_4 to T_3.

Several non-randomized studies have suggested that liquid formulations of levothyroxine or formulations in which the levothyroxine is dissolved in glycerin and encased in a gelatin capsule may circumvent the impaired absorption of levothyroxine that may occur with tablet preparations.[61] For patients receiving enteral feeding, liquid levothyroxine added directly to the feeding tube was associated with a similar serum TSH to that seen in another group of patients in whom the feeding was interrupted in order to administer crushed tablets.[62] The former procedure was found to be more convenient by providers. In a study of patients taking proton pump inhibitors, switching to an oral solution was associated with a decrease in serum TSH from a mean of 5.4 to 1.7 mIU/L, suggesting better absorption of the liquid preparation in these patients.[63] A study of patients with gastritis who had a stable serum TSH while taking levothyroxine tablets and were then switched to a lower dose of levothyroxine gel capsules showed that two-thirds of patients had a similar TSH on the lower dose, again suggesting better absorption of the gel capsule formulation.[64] In a double-blind, randomized, crossover trial of liquid thyroxine in 77 treatment-naive patients with hypothyroidism, no significant differences in thyroid function tests were seen when the liquid preparation was ingested at breakfast or 30 minutes before breakfast.[65] This could provide a solution for patients with difficulties ingesting levothyroxine before breakfast. If the findings of these studies are bolstered by randomized controlled studies in the future, these levothyroxine formulations may prove very convenient for hypothyroid patients. Alternatively, studies in adults with hypothyroidism suggest an equal efficacy of bedtime versus early morning intake of levothyroxine.[66]

Dosing and Administration

The average maintenance dose of levothyroxine for most adults is about 125 mcg/day.[53] The replacement dose of levothyroxine is affected by body weight. Estimates of weight-based doses for replacement in hypothyroid patients without any autonomous thyroid function include 1.6 and 1.7 mcg/kg/day, though hypothyroid patients still producing some thyroid hormone will require lower doses.[18] There is, however, a wide range of replacement doses, necessitating individualized therapy and appropriate TSH monitoring to determine an adequate but not excessive dose.

In addition to alleviation of symptoms, the goal of treatment for patients with hypothyroidism is to maintain the patient's TSH within the normal range. Some clinicians are of the opinion that the traditional reference range of approximately 0.5 to 4.5 mIU/L includes at its upper end some individuals who have unrecognized thyroid disease. Thus, some believe that the reference range should be modified downward to 0.5 to 3.5 mIU/L or even 0.5 to 2.5 mIU/L.[67] If this premise is accepted, both the TSH values that trigger L-thyroxine treatment and the TSH treatment goal could potentially be altered. There are cogent arguments on both sides of the issue. Those who suggest maintaining current reference ranges believe that lowering the upper limit of the reference range could result in treating many individuals with thyroid hormone who would not necessarily benefit from such treatment.[68] Those who favor narrowing the reference range suggest that additional patients would, in fact, derive benefit from thyroid hormone treatment.[67] There are calls by some for increasing the thyrotropin reference range specifically among individuals aged 80 years and older.[69] TSH reference ranges also differ for different populations, such as those who are pregnant, specific ethnic groups, and older individuals.[18]

The required dose of levothyroxine is dependent on the patient's age and the presence of associated disorders, as well as the severity and duration of hypothyroidism.[18] Most patients devoid of any thyroid function will require approximately 1.7 mcg/kg/day once they reach steady-state for full replacement. Dose requirement may be better estimated based on ideal body weight, rather than actual body weight. In patients with long-standing disease and older individuals without known cardiac disease, therapy should be initiated with 50 mcg daily of levothyroxine and increased after 1 month. The recommended initial daily dose for older patients with known cardiac disease is 25 mcg daily titrated upward in increments of 25 mcg at monthly intervals to prevent stress on the cardiovascular system. Some patients may experience an exacerbation of angina with higher doses of thyroid hormone. Although TSH is an indicator of under-replacement or over-replacement, clinicians often fail to alter the dose based on TSH values clearly outside of the normal range.

Subclinical hypothyroidism is a laboratory-defined phenomenon in which a patient has an elevated TSH level in the presence of a normal FT_4 level. Patients with subclinical hypothyroidism often complain of symptoms commonly seen in patients with overt hypothyroidism such as cold insensitivity, dry skin, fatigue, constipation, muscle cramps, poor memory, slowed thinking, and depression. However, up to a quarter of people with normal TSH levels report up to two of these symptoms, pointing to the nonspecific nature of these symptoms. An estimated 13 million people in the United States have subclinical hypothyroidism. Subclinical hypothyroidism progresses to overt hypothyroidism in 2% to 5% of patients per year.[70] The risk of progression is significantly greater in individuals with antibodies to thyroid peroxidase (TPO) and in those with higher baseline TSH levels. Levothyroxine therapy was not associated with a significant improvement in hypothyroid symptoms, fatigue, or quality-of-life in patients age 80 years or older with subclinical hypothyroidism.[71] These results argue against the routine use of levothyroxine for the treatment of subclinical hypothyroidism, particularly in the elderly. Thyroid hormone therapy was associated with lowering the mean thyrotropin value into the normal reference range compared with placebo but was not associated with improvements in general quality of life or thyroid-related symptoms.[72] While most patients with subclinical hypothyroidism can be observed without treatment, treatment may be indicated for patients with subclinical hypothyroidism and serum thyrotropin levels of 10 mU/L or higher, or for young and middle-aged individuals with subclinical hypothyroidism and symptoms consistent with mild hypothyroidism.[70]

Once euthyroidism is attained, the daily maintenance dose of levothyroxine does not fluctuate greatly. As patients age, the dosing requirement may be reduced.[18] Third-generation TSH assays improved the accuracy with which thyroid hormone replacement can be monitored. The TSH concentration is the most sensitive and specific monitoring parameter for adjustment of levothyroxine dose. Plasma TSH concentrations begin to fall within hours and are usually normalized within 2 weeks, but they may take up to 6 weeks for some patients, depending on the baseline value. Both TSH and T_4 concentrations are used to monitor therapy, and they should be checked every 6 weeks until a euthyroid state is achieved.[18] Laboratory assessment of thyroid function should be performed approximately 6 weeks after levothyroxine dose initiation or change. This time frame allows achievement of steady-state, as the half-life of levothyroxine is approximately 1 week. Serum T_4 concentrations can be useful in detecting noncompliance,

malabsorption, or changes in levothyroxine product bioequivalence, among other things.[73] An elevated TSH concentration indicates insufficient replacement. The appropriate dose maintains the TSH concentration in the normal range. T_4 disposal is accelerated by nephrotic syndrome, other severe systemic illnesses, and several antiseizure medications (phenobarbital, phenytoin, and carbamazepine) and rifampin. Pregnancy increases the T_4 dose requirement for 75% of women, probably because of factors such as increased degradation by the placental deiodinase, increased T_4 pool size, and transfer of T_4 to the fetus. The etiology of hypothyroidism also affects the magnitude of the dosage increase. Initiating postmenopausal hormone replacement therapy increases the dose needed in 35% of women, perhaps due to an increased circulating TBG level. Patient noncompliance with prescribed T_4, the most common cause of inadequate treatment, might be suspected for patients with a dose that is higher than expected, variable thyroid function test results that do not correlate well with prescribed doses, and an elevated serum TSH concentration with serum-free T_4 at the upper end of the normal range, which can suggest improved compliance immediately before testing, with a lag in the thyrotropin response.

For patients with central hypothyroidism caused by hypothalamic or pituitary failure, the serum TSH cannot be used to assess the adequacy of replacement. Alleviation of the clinical syndrome and restoration of serum T_4 to the normal range are the only criteria available for estimating the appropriate replacement dose of L-thyroxine. Keeping free T_4 values in the upper part of the normal laboratory reference range is a reasonable approach, with modification of this goal to the middle of the normal range in older patients or patients with comorbidities. Concurrent use of dopamine, dopaminergic agents (bromocriptine), somatostatin or somatostatin analogs (octreotide), and corticosteroids suppresses TSH concentrations in individuals with primary hypothyroidism and may confound the interpretation of this monitoring parameter.[18]

TSH-suppressive levothyroxine therapy can be given to patients with nodular thyroid disease and diffuse goiter, and to patients with a history of thyroid irradiation. It is also usually given to patients with papillary or follicular thyroid cancer. The rationale for suppression therapy is to reduce TSH secretion, which promotes the growth and function of abnormal thyroid tissue. However, such management, other than for patients with thyroid cancer or with elevated TSH levels, is quite controversial. Some clinicians rarely recommend or use such therapy; others will recommend a trial of levothyroxine as suppressive therapy in some patients. Three meta-analyses concluded that suppressive therapy for nodules was associated with a small decrease in nodule growth, a nonsignificant reduction in nodule growth, and a significant reduction in nodule growth with longer-term treatment. L-Thyroxine may be given in nontoxic MNG to suppress the TSH to low- normal levels of 0.5 to 1 mIU/L if the baseline TSH is more than 1 mIU/L. Goiter size and thyroid volume may be reduced with suppression therapy. Diffuse goiter associated with autoimmune thyroiditis may also be treated with levothyroxine to reduce goiter size and thyroid volume. If suppressive therapy with levothyroxine is pursued, the age, gender, and menopausal status of the patient need to be considered, along with the risk of cardiac arrhythmias and reduced bone mineral density. Levothyroxine suppression therapy is of benefit to all but the lowest-risk thyroid cancer patients and is generally used in the management of patients with differentiated thyroid cancer, with the TSH goal being influenced by the patient's thyroid cancer stage and other risk factors. Current guidelines from the ATA suggest suppressing the TSH to below 0.1 mIU/L in higher-risk patients but keeping TSH around the lower limit of normal (0.1-0.5 mIU/L) in low-risk patients.[74]

Special Populations

Myxedema Coma

Myxedema coma is a rare consequence of decompensated hypothyroidism.[8] Clinical features include hypothermia, advanced stages of hypothyroid symptoms, and altered sensorium ranging from delirium to coma. Mortality rates of 60% to 70% necessitate immediate and aggressive therapy. Traditionally, the initial treatment has been IV bolus levothyroxine 300 to 500 mcg.[18] However, as deiodinase activity is markedly reduced, impairing T_4 to T_3 conversion, initial treatment with IV T_3, or a combination of both hormones, has also been advocated.[8] Glucocorticoid therapy with IV hydrocortisone 100 mg every 8 hours should be given until coexisting adrenal suppression is ruled out.[18] All therapies must be administered parenterally as cessation of gastrointestinal peristalsis occurs, preventing the absorption of orally administered medications. Consciousness, lowered TSH concentrations, and improvement in vital signs are expected within 24 hours. Maintenance doses of levothyroxine are typically 75 to 100 mcg given IV until the patient stabilizes and oral therapy is begun. Supportive therapy must be instituted to maintain adequate ventilation, BP, and body temperature, and ensure euglycemia. Any underlying disorder which may have precipitated the event, such as sepsis or myocardial infarction, obviously must be diagnosed and treated.

Congenital Hypothyroidism

In congenital hypothyroidism, full maintenance therapy should be instituted early to improve the prognosis for mental and physical development. The average maintenance dose in infants and children depends on the age and weight of the child. Several studies demonstrate that aggressive therapy with levothyroxine is important for normal development, and current recommendations are for initiation of therapy as soon as possible after birth at a dose of 10 to 15 mcg/kg/day. This dose is used to keep T_4 concentrations at about 10 mcg/dL (130 nmol/L) within 30 days of starting therapy and is associated with improved IQs. The dose is progressively decreased to a typical adult dose as the child ages, with the adult dose given starting in puberty.

Hypothyroidism During Pregnancy

Hypothyroidism during pregnancy leads to an increased rate of stillbirths and possibly lower neuropsychological scores in infants born of women who received inadequate replacement during pregnancy.[38] Thyroid hormone is necessary for fetal growth and must come from the maternal side during the first 2 months of gestation. Although liothyronine may cross the placental membrane slightly better than levothyroxine, the latter is considered the drug of choice. The objective of treatment is to decrease TSH to normal, based on the normal reference range for pregnancy. Current guidelines suggest a TSH below 2.5 mIU/L during the first trimester and a TSH below 3 mIU/L during the remainder of the pregnancy.[38] Based on elevated TSH levels during pregnancy, the mean dose of levothyroxine had to be increased by 48% to decrease TSH into the normal range. However, in individual women, the dosage increase needed may vary from approximately 10% to 80%. Increased production of binding proteins, a marginal decrease in free hormone concentration, modification of peripheral thyroid hormone metabolism, and increased T_4 metabolism by the fetal-placental unit all may contribute to increased thyroid hormone demand. As these changes regress after delivery, the need for increased levothyroxine will decline.[38] Up to 60% of women need to have levothyroxine dose adjustment during pregnancy. An upward adjustment in the dose will usually be needed by the eighth week of pregnancy. Current guidelines recommend that hypothyroid patients receiving levothyroxine who become pregnant should increase their levothyroxine dose by 20% to 30% (two additional tablets weekly) as soon as they know they are pregnant.[38] After delivery the levothyroxine dose can be reduced based on T_4 concentrations and measurement of TSH, typically about 6 to 8 weeks after delivery. Many patients can return to their pre-pregnancy dose requirement.

EVALUATION OF THERAPEUTIC OUTCOMES—HYPOTHYROIDISM

Patients with idiopathic hypothyroidism and Hashimoto's thyroiditis on optimal thyroid hormone replacement therapy should have TSH and free T_4 serum concentrations in the normal range.[18] Those who are being treated for thyroid cancer should have TSH suppressed to low levels, with the appropriate TSH concentration being determined based on the patient's risk of recurrence or progression, and TG levels should be undetectable.[74] Given the 7-day half-life of T_4 and the potential delayed response of the hypothalamus, the appropriate monitoring interval for follow-up thyroid function testing is no more frequent than every 4 to 6 weeks. The signs and symptoms of hypothyroidism should be improved or absent (see Clinical Presentation of Hypothyroidism discussed earlier), although it may take several months for the full benefit of therapy to manifest.

CONCLUSION

Hypothyroidism is a common disorder but if left untreated it can progress into myxedema coma in the absence of an adequate endogenous thyroid reserve. Levothyroxine is a readily available and highly effective treatment that rapidly reverses the biochemical and clinical abnormalities that characterize hypothyroidism. Serum TSH and thyroid hormone levels are useful measures for adjusting the levothyroxine dose.

ABBREVIATIONS

anti-TPO Ab	anti-thyroid peroxidase antibody
ATD	antithyroid drug

AUC	area under the curve
BMI	body mass index
BP	blood pressure
cGy	centigray
C_{max}	maximum concentration
ClO_4^-	perchlorate
CNS	central nervous system
DIT	diiodotyrosine
FSH	follicle-stimulating hormone
FT_3	free triiodothyronine
FT_4	free thyroxine
Gsα	the α subunit of the stimulatory guanine-nucleotide–binding protein
hCG	human chorionic gonadotropin
HLA	human leukocyte antigen
^{131}I	sodium iodide-131
L-thyroxine	levothyroxine
LH	luteinizing hormone
MIT	monoiodotyrosine
MMI	methimazole
MNG	multinodular goiter
NHANES III	Third National Health and Nutrition Examination Survey
OTC	over the counter
PRTH	pituitary resistance to thyroid hormone
PTU	propylthiouracil
RAI	radioactive iodine
RAIU	radioactive iodine uptake

rT_3	reverse triiodothyronine
SCN^-	thiocyanate
SSKI	saturated solution of potassium iodide
T_3	triiodothyronine
T_4	thyroxine
TBG	thyroxine-binding globulin
TBII	TSH binding inhibitor immunoglobulin
TBPA	thyroid-binding prealbumin
TcO_4^-	pertechnetate
TG	thyroglobulin
TPOAb	thyroid peroxidase antibodies
TR	thyroid hormone receptor
TRH	thyrotropin-releasing hormone
TRIAC	triiodothyroacetic acid
TSAb	thyroid-stimulating antibody
TSH	thyroid-stimulating hormone
TT_3	total triiodothyronine
TT_4	total thyroxine
TTR	transthyretin
WBC	white blood cell

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SELF ASSESSMENT QUESTIONS

1. Which of the following signs or symptoms would lead you to suspect hyperthyroidism in a patient you are evaluating?
   A. Constipation
   B. Weight gain
   C. Depression
   D. Increased anxiety
2. Which of the following signs or symptoms would lead you to suspect hypothyroidism in a patient you are evaluating?
   A. Cold intolerance
   B. Increased appetite
   C. Palpitations
   D. Hyperreflexia
3. In a patient with primary hypothyroidism, which of the following thyroid function test results would you expect to find?
   A. Low FT_4, TT_3, and TSH levels
   B. Elevated FT_4, TT_3, and TSH levels
   C. Low FT_4 and TT_3 levels and elevated TSH levels
   D. Elevated FT_4 and TT_3 levels and low TSH levels
4. A cause of hyperthyroidism associated with a low radioactive iodine uptake (RAIU) scan is
   A. Graves' disease.
   B. Multinodular goiter.
   C. Thyroiditis.
   D. Toxic adenoma.
5. An otherwise well 43-year-old woman with recently diagnosed Graves' disease has decided to receive RAI therapy to definitively treat her hyperthyroidism. During the next 6 to 8 weeks prior to therapy, which of the following therapies is best avoided?
   A. A nonselective β-blocker
   B. Lugol's solution
   C. Methimazole
   D. Nadolol
6. Fred is a 40-year-old male who opts to receive drug therapy for the management of his hyperthyroidism secondary to a toxic multinodular goiter. Which of the following choices is the best therapy for his management?
   A. Lugol's solution 5 drops po TID

B. SSKI 3 drops po TID

C. Methimazole 10 mg po BID

D. PTU 100 mg po TID

7. Terry is a 59-year-old Caucasian female who has been treated with thyroid hormone replacement therapy for the last ten years for Hashimoto's thyroiditis. She states that she always takes her thyroid medication with breakfast and her refill records show that she always refills her T_4 on the 30th of the month. She has no other pertinent medical history. Two months ago she started medication for iron- deficiency anemia (iron sulfate 325 mg po TID with meals). Today's TSH level is 28 mIU/L(Reference Range: 0.4-4.0 mIU/L) despite her regular Synthroid dose of 125 mcg orally each morning. The most likely explanation of this patient's laboratory findings is

A. Noncompliance

B. Drug interaction.

C. Pregnancy.

D. Improper diagnosis.

8. George is a 46-year-old male with hyperthyroidism due to Graves' disease who has opted for methimazole therapy for management. The most important counseling advice he should receive is that

A. He has an approximate 33% chance of long-term remission of disease.

B. Methimazole is a better choice than PTU because of less hepatotoxicity.

C. Get a WBC count at the first sign of infection.

D. Take the medicine with food to minimize gastrointestinal upset.

9. Dotty is a 74-year-old, obese (100 kg) Caucasian female with a history of T2DM, hypertension, hyperlipidemia, atrial fibrillation, and coronary artery disease, who was recently diagnosed with hypothyroidism (numerous symptoms; FT_4 of 0.65 ng/dL (Reference Range: 0.7-1.9 ng/dL) or 8.4 pmol/L (Reference Range: 9-24.5 pmol/L); and a TSH of 43.4 mIU/L (Reference Range: 0.4-4.0 mIU/L) due to Hashimoto's thyroiditis. Her best initial thyroid hormone replacement strategy is

A. Armor Thyroid 3 grains orally once daily.

B. Cytomel 50 mcg orally twice/day.

C. Synthroid 175 mcg orally daily.

D. Tirosint 50 mcg orally daily.

10. Lucy is a 38-year-old woman with newly diagnosed Graves' disease, who experiences fatigue, heat intolerance, tremor, and palpitations. She has no significant medical history and is currently taking no medications. Laboratory results include the following: TSH less than 0.01 mIU/L (Reference Range: 0.4-4.0 mIU/L); FT_4 3.3 ng/dL (Reference Range:0.7-1.9 ng/dL) or 42.5 pmol/L (Reference Range: 9-24.5 pmol/L); and TT_3 368 ng/dL (Reference Range:80-180 ng/dL) or 5.67 nmol/L (Reference Range: 1.23-2.77 nmol/L). Initiation of which one of the following regimens will reduce her symptoms within hours?

A. PTU 100 mg three times/day

B. Methimazole 10 mg two times/day

C. Lugol's solution 10 drops three times/day

D. Nadolol 40 mg two times/day

11. Which of the following statements is true regarding liothyronine (synthetic T_3)?

A. It has a half-life of about one hour.

B. It is the treatment of choice for hypothyroidism.

C. It produces stable serum levels of both T_4 and T_3.

D. The side effects can include palpitations and insomnia.

12. Maggy is a 44-year-old woman with a history of papillary thyroid cancer who has always received the same generic levothyroxine replacement preparation since her thyroidectomy 4 years ago. Why is it important that she continue to receive the same T_4 preparation?

A. So she can save money.

B. So she won't need as many repeat thyroid function tests performed.

C. So she can maintain consistent TSH levels, which is important in reducing her risk of cancer recurrence.

D. She shouldn't continue on a generic; she should be switched to a branded T_4 preparation as this is a narrow therapeutic index drug.

13. Susan is a 40-year-old, 70-kg woman recently diagnosed with hypothyroidism (HoTR) due to Hashimoto's disease. She originally started levothyroxine 50 mcg orally once daily for 3 weeks, and for the last 2 weeks has received 100 mcg daily. The results of today's thyroid function tests (TFTs) are as follows: total thyroxine (TT_4) 3.5 mcg/dL (Reference Range: 5-12 mcg/dL) or 45 nmol/L (Reference Range: 64-154 nmol/L)], total triiodothyronine (TT_3) 56 ng/dL (Reference Range: 80-180 ng/dL) or 0.86 nmol/L (Reference Range: 1.23-2.77 nmol/L), and thyroid-stimulating hormone (TSH) 28 mIU/L (Reference Range: 0.4-4.0 mIU/L). Given these laboratory test results, which is the best recommendation for Susan's thyroxine (T_4) dose?

A. Decrease her dose because her TSH level is high.

B. Increase her dose because her total T_4 (TT_4) and total T_3 (TT_3) values are low.

C. Make no change because steady state has not been reached on this dose.

D. Make no change because her free T_4 (FT_4) value is not available.

14. Which of the following therapies is *inappropriate* for the treatment of thyroid storm?

A. Administering a β-blocker as initial therapy

B. Administering SSKI as initial therapy

C. Administering PTU as initial therapy

D. Administering methylprednisolone as initial therapy

15. Which of the following statements is true regarding the treatment of myxedema coma?

A. High-dose oral liothyronine is most effective.

B. Oral levothyroxine is the mainstay of therapy.

C. β-Blockers are routinely administered.

D. Intravenous thyroid hormone replacement is advisable.

SELF-ASSESSMENT QUESTIONS-ANSWERS

1. **D.** Hyperthyroidism represents a hypermetabolic state. The typical clinical manifestations of thyrotoxicosis include nervousness, anxiety (answer D), palpitations, easy fatigability, menstrual disturbances, and heat intolerance. A cardinal sign is a loss of weight concurrent with an increased appetite. Constipation, weight gain, and depression (choices A, B, and C) are common manifestations of hypothyroidism. See Clinical Presentation—Thyrotoxicosis.

2. **A.** Hypothyroidism represents a hypometabolic state, with typical signs and symptoms including dry skin, cold intolerance (answer A), weight gain, constipation, and weakness. Complaints of lethargy, depression, fatigue, exercise intolerance, or loss of ambition and energy are also common but are less specific. Increased appetite, palpitations, and hyperreflexia (choices B, C, and D) are common manifestations of hyperthyroidism. See Clinical Presentation—Hypothyroidism.

3. **C.** Primary hypothyroidism refers to a lack of thyroid hormone synthesis as a result of loss of function of the thyroid gland itself. This results in low FT_4 and TT_3 levels. Consequently, TRH and TSH secretion is increased in an attempt to stimulate the failing thyroid gland to make more T_3 and T_4. Therefore, answer C is correct. See Table 92-4.

4. **C.** A radioactive iodine uptake (RAIU) tests thyroid function by measuring how much radioactive iodine is taken up by the thyroid gland over a certain time period (6 hours and 24 hours). This test is often ordered for patients with symptoms of thyrotoxicosis to help identify the specific cause of hyperthyroidism. Causes of thyrotoxicosis associated with an elevated RAIU include Graves' disease, multinodular goiter, toxic adenoma (choices A, B, and D), trophoblastic diseases, and a TSH-secreting tumor. Common causes of thyrotoxicosis associated with a low RAIU include thyroiditis (answer C), iodide ingestion, and ingestion of exogenous thyroid hormone. See text under Causes of Thyrotoxicosis Associated with Suppressed RAIU.

5. **B.** Most hyperthyroid patients opting for definitive therapy (surgery, RAI) will be pretreated for 6 to 8 weeks prior to the procedure to reduce HTR symptoms and to prevent thyroid storm as a result of the definitive procedure. All of the listed choices are potential treatments for Graves' disease. Nadolol (choice D) is a non-selective β-blocker (choice A) and is associated with prompt (within hours) reduction of many hyperthyroid symptoms and will not interfere with RAI therapy. Methimazole (choice C) is a thioamide and inhibits organification and coupling but does not affect stored thyroid hormone values; thus, several weeks are required before a reduction in HTR symptoms is evident. It is generally used for 6 to 8 weeks prior to surgery or RAI and then stopped 3 to 4 days prior to RAI therapy. Lugol's solution (Answer B) contains iodide; iodides given prior to RAI therapy will prevent uptake of the RAI by the thyroid gland (Wolff–Chaikoff mechanism), rendering its use ineffective.

6. **C.** Iodide therapy (choices A and B) is used to decrease the release of stored thyroid hormone but is not used in patients with autonomous thyroid disorders (uninodular or multinodular disease) as these tissues will subsequently use the iodine to make new thyroid hormone, further exacerbating the hyperthyroidism. Thioamides decrease the production of new thyroid hormones by inhibiting organification and coupling. Methimazole (choice C) is preferred over propylthiouracil (PTU) because of the decreased incidence of hepatotoxicity.

7. **B.** The patient has a 10-year history of thyroid disease, dutifully picks up prescriptions each month, and is 59 years old, thereby making choices A, C, and D unlikely. Levothyroxine is approximately 80% bioavailable but its absorption can be decreased by food and medications. Di- and trivalent cations (calcium, magnesium, aluminum, iron) are well known to markedly decrease the absorption of T_4 unless the T_4 is taken 1 hour prior or at least 4 hours after the interacting medication. The patient has been taking her T_4 and morning iron dose together for the last two months and now has an elevated TSH level, making choice B the correct answer.

8. **C.** All of the above choices are correct statements. However, choice C is the best answer as there is the possibility of life-threatening drug-induced agranulocytosis with the use of thioamide therapy. Patients should be advised to have a white blood cell (WBC) count with differential performed at the first sign of an infection (sore throat, fever) to rule out agranulocytosis after starting thioamide therapy.

9. **D.** T_4 is the generally recommended thyroid hormone of choice as it is stable, pure, and has predictable potency; serum T_3 concentration is

controlled physiologically (less likelihood of HTR-like adverse effects compared with T_3 formulations or T_4/T_3 combination products); and it has a long half-life, allowing once-daily dosing. The typical maintenance dose of T_4 required in patients without endogenous thyroid function is approximately 1.6 to 1.7 mcg/kg. However, replacement therapy is typically initiated at a lower dose to minimize the risk of untoward events, such as precipitation of arrhythmias or cardiac ischemia. The four choices listed are equivalent to approximately 180, 240, 175, and 50 mcg of T_4, respectively. As this patient has a history of atrial fibrillation and coronary artery disease, a modest dose of T_4 should be initiated and then titrated as tolerated, making choice D the correct answer.

10. **D.** It takes weeks for thioamides (answers A and B) to have an effect because they inhibit the formation of new thyroid hormone but do nothing to reduce stored thyroid hormone levels. Lugol's solution (Answer C) inhibits the release of stored thyroid hormone. Symptom relief is seen much sooner than with the thioamides but only after circulating thyroid hormone values significantly decrease (T_4 half-life is about 7 days in a euthyroid patient). β-Blockers begin to manage sympathetic-mediated symptoms immediately.

11. **D.** Liothyronine has a half-life of approximately one day (not 1 hour), it is not converted to T_4 (T_4 is converted peripherally to T_3), and levothyroxine is the treatment of choice for hypothyroidism, making choices A, B, and C incorrect. Once-daily dosing of liothyronine produces high-peak (and low-trough) levels of the drug in the serum, contributing to side effects associated with signs and symptoms of hyperthyroidism. Therefore, choice D is correct.

12. **C.** An individual patient is recommended to continue to use the same brand or generic version of levothyroxine as T_4 is a narrow therapeutic index drug. While the bioavailability of different brand and generic preparations is considered bioequivalent (the FDA considers a range of 80%-125% of *C*max, *T*max, and AUC equivalent), there may be enough differences to affect subsequent TSH levels. This patient would typically be dosed to maintain a low TSH level (eg, 0.1-1.0 mIU/L) in order to decrease the likelihood of recurrence of her papillary thyroid cancer. If this patient were switched to a T_4 product with less bioavailability, her TSH level would rise, increasing the risk of thyroid cancer recurrence. If this patient is switched to a T_4 product with greater bioavailability, this would likely result in symptoms of over-replacement (hyperthyroidism). While choices A, B, and C are all true statements, choice C is the best answer to the question. Often such patients will be prescribed a branded T_4 preparation as it is easier to ensure the use of the same T_4 preparation. However, consistently using the same generic T_4 preparation is appropriate; thus, choice D is incorrect.

13. **C.** Susan has primary HoTR; hence, an elevated TSH level indicates under-replacement of therapy (not over-replacement—choice A). The current low TT_4 and TT_3 levels (choice B) are not reflective of her final thyroid hormone levels at steady-state. Susan has received 5 weeks of T_4 replacement therapy but has received only 2 weeks of therapy at the present dose of 100 mcg daily. Steady state is reached in 4 to 5 half- lives and the half-life of T_4 is approximately 1 week. Re-equilibration of TSH based on the steady-state levels of FT_4 and TT_3 levels will take an additional 1 to 2 weeks; therefore, Susan should make no change in her current T_4 dose and have FT_4 and THS levels checked in another 4 to 5 weeks.

14. **B.** Thyroid storm is a life-threatening medical emergency characterized by decompensated thyrotoxicosis, high fever, tachycardia, tachypnea, dehydration, delirium, coma, nausea, vomiting, and diarrhea. Even with aggressive treatment, the mortality rate is approximately 20%. Prompt initiation of therapy aimed at the suppression of thyroid hormone formation and secretion, antiadrenergic therapy, administration of corticosteroids, and treatment of associated complications or coexisting factors that may have precipitated the storm is indicated (see Table 96-7). While all of the above medications are typically indicated for treatment, iodide (SSKI and Lugol's solution) should be administered after thioamide is to inhibit iodide utilization by the overactive gland. If iodide is administered first, it could theoretically provide a substrate to produce even higher levels of thyroid hormone.

15. **D.** Myxedema coma is an example of decompensated hypothyroidism and includes hypothermia, advanced stages of hypothyroid symptoms, and altered sensorium ranging from delirium to coma. Mortality rates of 60% to 70% necessitate immediate and aggressive therapy. Traditionally, the initial treatment has been IV bolus levothyroxine 300 to 500 mcg. However, as deiodinase activity is markedly reduced, impairing T_4 to T_3 conversion, initial treatm ent with intravenous T_3, or a combination of both hormones has also been advocated. Glucocorticoid therapy with IV hydrocortisone 100 mg every 8 hours should be given until coexisting adrenal suppression is ruled out. All therapies must be administered parenterally as cessation of gastrointestinal peristalsis occurs, preventing the absorption of orally administered medications. β-Blockers are

typically indicated in thyroid storm but are contraindicated in myxedema coma.