Chapter 100: Thyroid Disorders

Kathleen J. Pincus; Rachel W. Khan

KEY CONCEPTS

KEY CONCEPTS

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

2. Hyperthyroidism may be treated with antithyroid drugs such as methimazole or propylthiouracil, 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, cardiovascular disease), and patient preference.

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

4. Response to methimazole and propylthiouracil 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 RAI rather than undergo repeated courses of methimazole or propylthiouracil 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.

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 the patient experience with hyperthyroidism and hypothyroidism, visit the British Thyroid Foundation's Patient Stories webpage: https://www.btf-thyroid.org/pages/category/patient-stories

INTRODUCTION

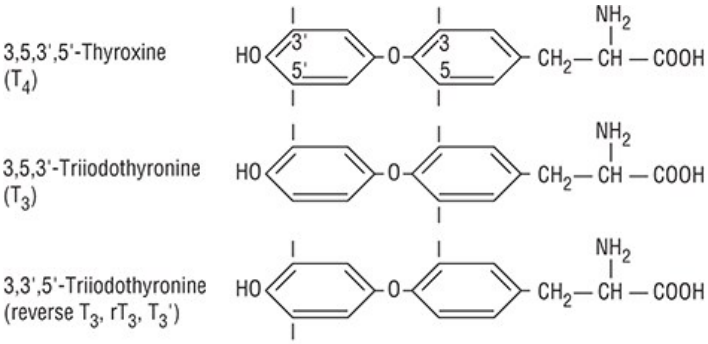
Thyroid hormones influence nearly every organ system in the body. Thyroid hormones influence metabolism, body temperature, heart rate, cholesterol, appetite, weight, intestinal motility, mood, menstrual cycles, gluconeogenesis, breathing, central and peripheral nervous systems, muscle strength, skin, and hair. Multiple levels of biofeedback and regulation allow the body to maintain normal thyroid hormone levels under many conditions. When thyroid hormone levels are outside of normal ranges, symptoms can be multisystemic, variable, and nonspecific.

Thyroid Hormone Synthesis

The synthesis of thyroid hormones thyroxine (T_4) and triiodothyronine (T_3) involves four key molecules: iodine, thyroglobulin (TG), thyroid peroxidase (TPO), and hydrogen peroxide (H_2O_2) (Fig. 100-1). Iodine is an essential element supplied through dietary intake and absorbed in the gastrointestinal tract. The recommended dietary allowance for nonpregnant adults is 150 mcg/day. Small amounts of iodine are necessary for thyroid hormone synthesis, but large amounts can inhibit their production and release. Iodide (I^-), the ionic form of iodine, is readily taken up and stored in the thyroid gland via active transport by the Na^+/I^- symporter (NIS) against an electrochemical gradient driven by the coupled transport of sodium. This results in an iodide concentration in thyroid follicular cells that is up to 400 times higher than serum iodide concentrations. Thyroid-stimulating hormone (TSH) stimulates iodide uptake. Structurally related anions, including thiocyanate (SCN^-), perchlorate (ClO_4^-)(C1O4−), pertechnetate (TcO_4^-)(TcO4−), bromine, fluorine, and, under certain circumstances, lithium competitively inhibit iodine transport (Table 100-1).

FIGURE 100-1

Structure of thyroid hormones.



Source: Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, Lisa M. Holle, Jennifer Cocohoba, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 13th Edition*

TABLE 100-1

Thyroid Hormone Synthesis and Secretion Inhibitors

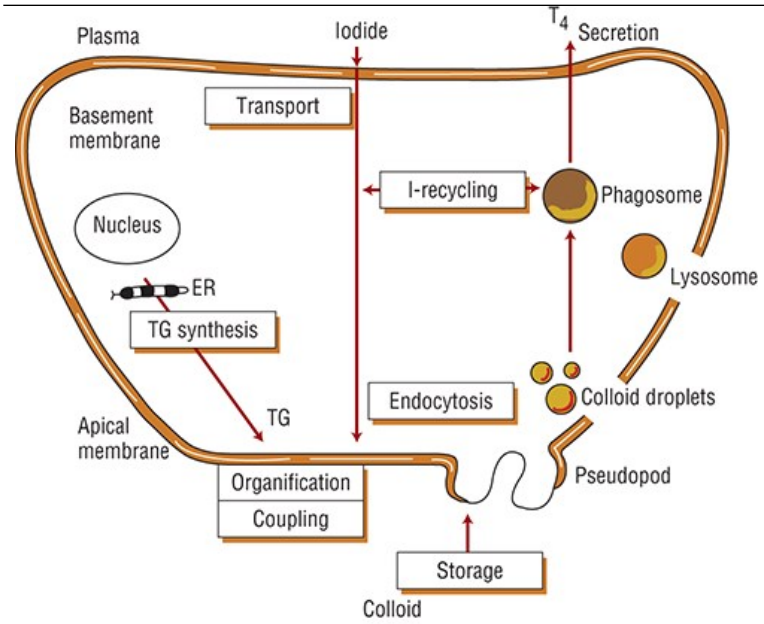
Mechanism of Action	Substance
Blocks iodide transport into the thyroid	• Bromine • Fluorine • Lithium
Impairs organification and coupling of thyroid hormones	• Thionamides • Sulfonamide • Salicylamide • Antipyrine
Inhibits thyroid hormone secretion	• Iodide (large doses) • Lithium

TG is a large molecular weight glycoprotein that stores iodine and facilitates the coupling reactions involved in thyroid hormone synthesis. TPO is the key enzyme that catalyzes iodine oxidation to promote thyroid hormone synthesis. H_2O_2 oxidizes TPO to its active form. TSH stimulates H_2O_2 production and gene expression of both TG and TPO. Oxidized iodine provides negative feedback on TPO expression and H_2O_2 production.

During thyroid hormone synthesis, H_2O_2 oxidizes TPO to its active form (Fig. 100-2). TPO, in turn, oxidizes iodide ions that have been transported into the thyroid follicular cell through active transport. The oxidized iodide ions then bind to TG, creating iodinated TG. A series of coupling reactions occur within the iodinated TG molecule, which include transferring iodophenoxyl groups from monoiodotyrosine (MIT) and diiodotyrosine (DIT) moieties to DIT moieties to form an unstable compound that decomposes into T_3 or T_4 and dehydroalanine within the TG molecule. When two molecules of DIT combine, T_4 is formed, whereas MIT and DIT constitute T_3 (Fig. 100-3). T_3, T_4, and iodide are released from TG via proteolysis. Some T_4 is converted to T_3 within the thyrocyte by deiodinase type 1 and type 2. T_3 and T_4 are released into the bloodstream via transporters, a step that can be inhibited by lithium or excessive iodine concentrations. Iodide is recycled, creating a reservoir of intrathyroidal iodide.

FIGURE 100-2

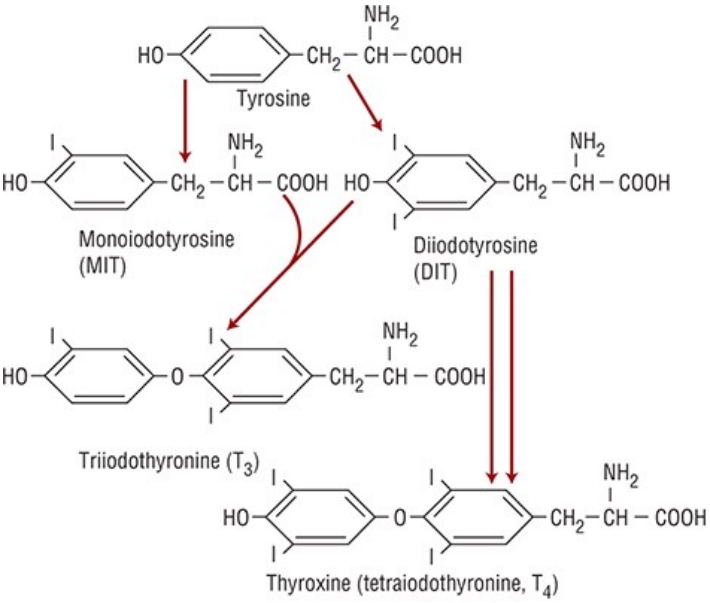
Thyroid hormone synthesis. Iodide is transported from the plasma, through the cell, to the apical membrane, where it is organified and coupled to the thyroglobulin (TG) synthesized within the thyroid cell. Hormone stored as colloid reenters the cell through endocytosis and moves back toward the basal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



Source: Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, Lisa M. Holle, Jennifer Cocohoba, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 13th Edition*

FIGURE 100-3

Scheme of coupling reactions.



Source: Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, Lisa M. Holle, Jennifer Cocohoba, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 13th Edition*

Thyroid Hormone Regulation and Action

Thyroid hormones produce physiologic effects through binding to nuclear thyroid hormone receptors (TRs). TRs regulate the transcription of target genes in the presence of physiologic concentrations of T_3. Unlike most other nuclear receptors, TRs also actively regulate gene expression in the

absence of hormones, 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. 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.

Production of T_3 and T_4 is regulated through the hypothalamic-pituitary axis. The hypothalamus detects small changes in peripheral T_3 and T_4 levels and regulates the release of thyrotropin-releasing hormone (TRH) accordingly. TRH acts on the anterior pituitary gland to regulate the release of TSH, also called thyrotropin, which binds to thyrotropin receptors in the thyroid gland. The thyrotropin receptor belongs to the family of G-protein–coupled receptors. Activation of thyrotropin receptors stimulates the expression of NIS, TG, and TPO genes and increases iodide uptake into the thyrocyte. Through these actions, increased TSH levels lead to increased production of T_3 and T_4 in normally functioning thyroid glands. In turn, increased circulating levels of T_3 and T_4, through a negative feedback effect, down-regulate the production of TRH by the hypothalamus and TSH by the pituitary.

Mutations of the thyrotropin receptor can lead to hypothyroid or hyperthyroid presentations. Activating thyrotropin receptor mutations have been found in patients with autonomously functioning thyroid nodules, Leclere syndrome, and McCune–Albright syndrome. Conversely, thyrotropin resistance results from point mutations that prevent TSH binding, as seen in congenital hypothyroidism. Individuals with this abnormality have high levels of TSH but decreased TG levels and a normal or small thyroid gland.

T_3 is four times more potent and has a 10- to 15-fold higher binding affinity at TRs compared to T_4. However, T_3 is available in lower serum concentrations and has a shorter half-life than T_4. Both hormones are highly protein-bound, with only unbound hormones (free T_3 [FT_3] and free T_4 [FT_4]) being biologically active. Both T_3 and T_4 are produced directly from the thyroid gland, but less than 20% of circulating T_3 is produced in the thyroid.

Another level of thyroid hormone regulation occurs at the level of T_4 to T_3 conversion by deiodinase enzymes in the periphery. The majority of T_3 (75%-80%) is produced through peripheral conversion from T_4 through monodeiodinase enzymes. The activity of deiodinase enzymes, and subsequently the rate of T_4 to T_3 conversion, is regulated by a variety of factors including nutrition, nonthyroidal hormones, ambient temperatures, drugs, and illness.

Three different monodeiodinase enzymes are present in the body (Table 100-2). Monodeiodinase type I enzymes are present in peripheral tissues such as the liver and kidney, whereas type II enzymes are found in the central nervous system, pituitary, and thyroid. Type III enzymes, found in the placenta, skin, and developing brain, inactivate T_4 and T_3. During the enzymatic conversion of T_4, T_3 or reverse T_3 may be formed. Reverse T_3 is biologically inactive and accounts for a small component of hormone metabolism. During coupling reactions, iodine deficiency causes an increase in the MIT:DIT ratio in TG and leads to a relative increase in the production of T_3 compared to T4. Because T_3 is more potent than T_4, the increase in T_3 production in iodine-deficient areas may be beneficial. 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 FT_3 to FT_4.

TABLE 100-2

Properties of Iodothyronine 5′-Deiodinase Isoforms

Property	Type I	Type II	Type III
Tissue localization	Kidney, liver, pituitary, thyroid	Brain, brown adipose tissue, pituitary, skeletal muscle, thyroid	Brain, fetus, placenta, skin, uterus
Preferred substrate	T_3 and rT_3	T_4 and rT_3	T_3 and T_4
Physiologic or pathophysiologic role	Clearance of T_3 and rT_3 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
Susceptibility to propylthiouracil	High	Low	Low

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

Several thyroid disorders result from the production of autoimmune antibodies affecting thyroid hormone synthesis and activity. These include thyroglobulin antibodies (TgAb), thyroperoxidase antibodies (TPOAb), and thyrotropin receptor antibodies (TRAb). TPOAb and TgAb can lead to the destruction of thyroid cells and diminished production of thyroid hormone. The initial action of TPOAb or TgAb can trigger the release of preformed thyroid hormone and an initial hyperthyroid presentation before thyroid gland destruction in a subset of patients. TRAbs act on TSH receptors, usually stimulating increased thyroid hormone production, though occasionally TRAbs have inhibitory effects. The presence of thyroid antibodies occurs in up to 20% of people without thyroid disorders. However, detection, along with clinical presentation, can help direct diagnosis and treatment in patients with altered thyroid hormone production.

HYPERTHYROIDISM AND THYROTOXICOSIS

Thyrotoxicosis results when tissues are exposed to inappropriately high levels of T_4, T_3, or both. Hyperthyroidism, which is one cause of thyrotoxicosis, refers specifically to the overproduction of thyroid hormone by the thyroid gland. Hyperthyroidism may be classified as overt or subclinical. Overt hyperthyroidism is identified by serum TSH values below the reference range combined with elevated serum T_3 and FT_4 concentrations plus symptoms of thyrotoxicosis. Subclinical hyperthyroidism constitutes serum TSH values below the reference range in the setting of normal serum values of T_3 and FT_4 and in the absence of symptoms.

EPIDEMIOLOGY—THYROTOXICOSIS

The prevalence of hyperthyroidism in the United States is less than 2%. The prevalence of suppressed TSH values follows a bimodal distribution, with a peak in people aged 20 to 39 and then again in those 80 or older. Abnormal TSH levels are 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 100-3). Note that RAIU is contraindicated in patients who are pregnant or lactating. The normal 24-hour RAIU ranges from 10% to 30% with some regional variation, depending on iodine intake. An elevated RAIU indicates that the patient's thyroid gland is actively overproducing T_4, T_3, or both. Hyperthyroidism from overactive thyroid gland is most commonly due to Graves' disease or nodular thyroid disease. Measurement of TRAbs can be a quicker diagnostic test for Graves' disease. 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.

TABLE 100-3

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

Increased RAIU[a]	Decreased RAIU
TRAb (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

hCG, human chorionic gonadotropin; RAIU, radioactive iodine uptake; TRAb, thyrotropin receptor antibody.

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

The underlying etiology dictates possible treatment options. 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. 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 may be present depending on the phase of the illness.

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) offer pain relief. 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 human leukocyte antigen (HLA)-DR3 and DR5 in patients with painless thyroiditis; nonendocrine autoimmune diseases are also more common. Drugs such as interferon-alpha, tyrosine kinase inhibitors, and lithium have also been implicated. 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 not tender.

The 24-hour RAIU will typically be suppressed to less than 2% during the thyrotoxic phase of painless thyroiditis. TgAb and 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 β-blockers. Like painful subacute thyroiditis, ATDs are not indicated because they do not decrease the release of preformed thyroid hormone.

Exogenous Thyroid Hormone

Thyrotoxicosis factitia is hyperthyroidism due to the ingestion of thyroid hormone. This category includes hyperthyroidism produced by the intentional ingestion of exogenous thyroid hormone, oftentimes to promote weight loss. 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, pharmacy error, or ingestion of food sources contaminated with thyroid tissue.

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.

Medications Containing Iodine

Amiodarone may induce thyrotoxicosis, overt hypothyroidism, subclinical hypothyroidism, or euthyroid hyperthyroxinemia, depending on the underlying thyroid function and pathology. 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 iodine overload, iodine-exacerbated thyroid dysfunction commonly occurs among 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 iodine-induced hyperthyroidism (type 1), destructive thyroiditis also occurs (type 2), 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 1 amiodarone-induced hyperthyroidism responds somewhat to thionamides, whereas type 2 may respond to

glucocorticoids. Radioactive iodine (RAI) therapy is inappropriate in type 1 due to the drug-induced iodine excess and in type 2 due to lack of increased hormone synthesis. Rarely, thyroidectomy is an option in select patients unresponsive to drug therapy. 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 deiodinase, leading to reduced conversion of T_4 to T_3 and hyperthyroxinemia without thyrotoxicosis (ie, elevated serum total T_4 and T_3 with normal TSH).

High intake of biotin can interfere with thyroid hormone assays, leading to false thyroid function test results. Excess biotin leads to falsely elevated results of total T_4, FT_4, and total T_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 at least 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 RAI scanning. Treatment with RAI 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 scanning. 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.

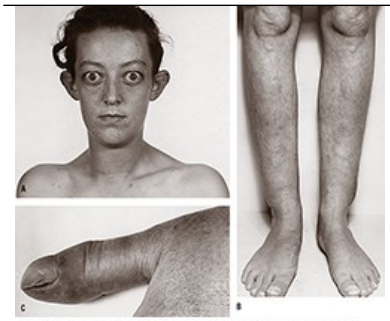
Causes of Thyrotoxicosis Associated with Elevated RAIU

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. 100-4). 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 TRAbs, 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 100-4

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.)*



Source: Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, Lisa M. Holle, Jennifer Cocohoba, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 13th Edition*

There is now compelling evidence that genetic heredity predisposes the susceptible individual to the development of clinically overt autoimmune thyroid disease in the setting of environmental and hormonal triggers. The role of sex hormones in the emergence of Graves' disease is suggested by the fact that hyperthyroidism is approximately eight times more common in women than in men. Monozygotic twins have a 35% likelihood of developing the disease compared with a 3% likelihood for a dizygotic twin. Thus, 79% of the predisposition to Graves' disease is genetic. Other autoimmune diseases, including Hashimoto's thyroiditis, also show an increased occurrence in families of patients with Graves' disease. Polymorphisms in HLA-DR, genetic mutations in thyroglobulin and thyrotropin receptor, and other immunomodulatory players confer an increased risk of 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 physical exam can be very telling of Graves' disease. 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. 100-4). Graves' ophthalmopathy (also called Graves' orbitopathy and thyroid-eye disease) is an inflammatory eye disease that occurs in association with autoimmune thyroid disorders. A major risk factor for developing or worsening Graves' ophthalmopathy is smoking, and smoking cessation or avoidance should be advised for all patients with Graves' disease. In rare but severe cases, Graves' ophthalmopathy can be sight-threatening. An important clinical feature of Graves' disease is the occurrence of spontaneous remissions, albeit uncommon. The abnormalities in TRAb 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 100-4). 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 FT_4 and FT_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 100-4

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 FT_4, total T_4, total T_3, and TSH concentrations will confirm the diagnosis of thyrotoxicosis. Obtaining TRAb in patients with a nonnodular thyroid and mild/no exophthalmos may help rule in Graves' disease versus other etiologies of thyrotoxicosis. Newer generation bioassays have excellent specificity and sensitivity for Graves' disease. People of Asian and Hispanic ancestry may have a rare form of thyrotoxicosis from hypokalemic periodic paralysis. 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. Treatment for overt Graves' hyperthyroidism can be any of the following: RAI, ATDs, or thyroidectomy.

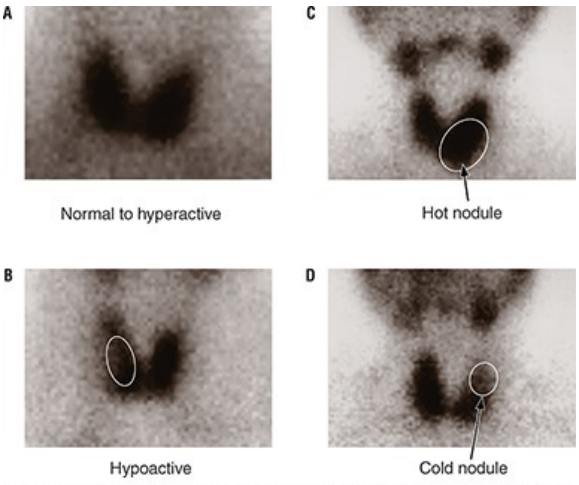
Toxic Adenoma

Toxic adenomas are benign tumors that produce thyroid hormones independently of pituitary and TSH control. They arise from activating somatic mutations of the TSH receptor or, less commonly, the Gsα protein; more than a dozen TSH receptor mutations have been described. The prevalence of toxic adenoma ranges from about 2% to 9% of thyrotoxic patients and depends on iodine availability and geographic location. 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. 100-5). The amount of thyroid hormone produced by an autonomous nodule is mass-related. Therefore, hyperthyroidism usually occurs when nodules are larger 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 the 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 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 the induction of thyroid cancer. However, thyroid cancer has rarely been associated with RAI therapy. Furthermore, compared to other treatment options (ie, thionamides or surgery) RAI therapy does not appear to increase the risk of solid cancer mortality. Among those receiving RAI therapy, the risk of solid cancer mortality may be dose-dependent. An autonomously functioning nodule, if not large enough to cause thyrotoxicosis, can often be managed conservatively without therapy.

FIGURE 100-5

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.)



Source: Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, Lisa M. Holle, Jennifer Cocohoba, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 13th Edition*

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 advanced age. Any unexplained chronic illness in an older adult presenting with an MNG calls for the exclusion of hidden (silent) thyrotoxicosis. 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 the 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 biological activity and must combine 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 TSH concentrations. Because the pituitary gland is extremely sensitive to minimal elevations of FT_4, a "normal" or elevated TSH level in a patient with elevated FT_4 indicates the inappropriate production of TSH. These rare disorders resulting from TSH overproduction are classified as "central hyperthyroidism."

TSH-Secreting Pituitary Adenomas

TSH-secreting pituitary tumors occur sporadically and release a biologically active hormone that is unresponsive to normal feedback control. In 30% of cases, the 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. In contrast to TSH-secreting pituitary adenomas, PRTH will show an appropriate increase in TSH in response to TRH and TSH suppression 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 been associated with central hypothyroidism in those euthyroid at baseline and may have therapeutic benefits in PRTH.

CLINICAL PRESENTATION THYROTOXICOSIS

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.

- Symptoms of thyrotoxicosis may be seen in multiple organ systems:
  - Cardiac: palpitations, atrial fibrillation
  - Gastrointestinal: increased bowel movements, weight loss (anorexia in severe disease and older adults)
  - Nervous system: nervousness, anxiety, emotional lability
  - Menstrual cycles: scant or irregular menses
  - Musculoskeletal: proximal muscle weakness, bone mineral density loss (in long-term hyperthyroidism)
- Extremely thyrotoxic patients (a presentation described as a thyroid storm) may have tachycardia, heart failure, psychosis, hyperpyrexia, and coma.

Signs

- Thyroid exam may be normal or may reveal enlarged thyroid gland (thyromegaly).
- Signs of thyrotoxicosis may be evident in multiple organ systems:
  - Cardiac: tachycardia at rest, widened pulse pressure, systolic ejection murmur
  - Nervous system: fine tremor of the protruded tongue and outstretched hands
  - Musculoskeletal system: hyperactive deep tendon reflexes
  - Face: exophthalmos (in Graves' disease only), eyelid retraction, lagging of the upper lid behind the globe when the patient looks downward (lid lag)
  - Skin, Nails, and Hair: warm, smooth, moist skin, pretibial myxedema (in Graves' disease only), unusually fine hair, separation of the end of the fingernails from the nail beds (onycholysis)
- Older adult 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

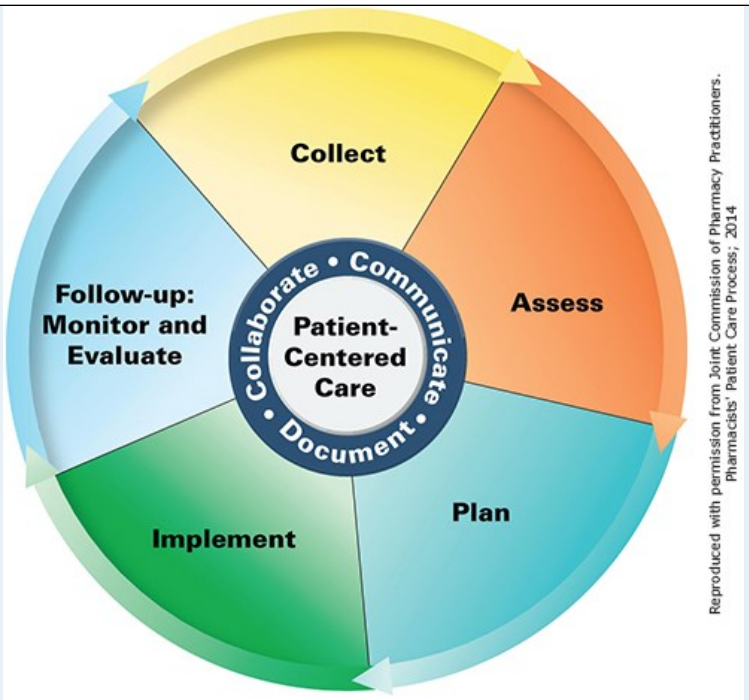
- Low TSH serum concentration. Elevated free and total T_4 and T_3 serum concentrations, particularly in more severe disease.
- Elevated RAIU by the thyroid gland when the hormone is being overproduced; suppressed RAIU in thyrotoxicosis due to thyroid inflammation (thyroiditis).

Other Tests

- TG
- TRAbs

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)
- History of present illness including 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)
  - Physical exam (eg, thyroid gland tenderness, symmetry, and nodularity)
  - Labs (eg, FT_4, total T_3, TSH, thyroid-stimulating antibodies; serum electrolytes, Scr, ALT)
  - Other diagnostic tests when indicated (eg, thyroid ultrasound, RAIU scan)

Assess

- Cause of hyperthyroidism (see Table 100-3)
- 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 100-5)

- Monitoring parameters including efficacy (eg, resolution of signs and symptoms) and safety (symptomatic hypothyroidism, adverse effects of medications), laboratory tests (TSH, FT_4, total T_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
- Follow-up laboratory monitoring

****Collaborate with patient, caregivers, and other healthcare professionals.***

TREATMENT

Thyrotoxicosis

2 Three common treatment modalities are used in the management of hyperthyroidism: surgery, ATD, and RAI (Table 100-5).

TABLE 100-5

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 • Medication adherence	• 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 sex, the existence of nonthyroidal conditions, and response to previous therapy. 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. Patient preference, after appropriate counseling, is essential to decision-making. Treatment options can be broadly categorized as those that target acute manifestations of thyrotoxicosis (eg, adrenergic blockers, iodides) and those that target the underlying cause of hyperthyroidism (eg, thionamides, RAI, surgery). Clinical guidelines for the treatment of hyperthyroidism have been published. Selected recommendations from these guidelines are shown in Table 100-6.

TABLE 100-6

Selected Recommendations from the American Thyroid Association Hyperthyroidism Guidelines

Question	Synopsis or Paraphrase of Recommendation	Grading
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/min or coexistent cardiovascular disease.	Strong recommendation, moderate quality
If RAI 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 white blood cell (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, moderate 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, low 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 methimazole, RAI therapy, or thyroidectomy. RAI therapy should be	Strong

be managed in children and adolescents?	avoided in 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. Propylthiouracil should be used when ATD therapy is given during the first trimester. Methimazole 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, FT_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

GD, Graves' disease; RAI, radioactive I-131; TMNG, toxic multinodular goiter; TA, toxic adenoma; SH, subclinical hyperthyroidism; WBC, white blood cell.

Data from Reference: Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, Maia AL, Rivkees SA, Samuels M, Sosa JA, Stan MN, Walter MA. 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. Thyroid 2016;26(10):1343–1421. DOI:10.1089/thy.2016.0229.

Nonpharmacologic Therapy

Surgery is an option for many causes of thyrotoxicosis. It should be strongly considered for patients with a large thyroid gland (at least 80 g), severe ophthalmopathy, documented or suspected thyroid malignancy, and coexisting primary hyperparathyroidism requiring surgery. In MNG, surgery is preferred over RAI in cases of cosmetic issues or pressure symptoms. 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. Surgery may be an alternative in the case of lack of remission on antithyroid drug treatment. Thyroidectomy should only be considered in pregnancy when rapid control of hyperthyroidism is required, and ATDs are not an option. It is best to avoid performing the surgery during the first and third trimesters of pregnancy owing to the risks to the fetus. Appropriate preparation of the patient for thyroidectomy includes methimazole until the patient is biochemically euthyroid (usually 6-8 weeks), followed by the addition of iodides 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. 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%). Hypothyroidism is certain after total thyroidectomy.

Therapeutic plasmapheresis is an effective alternative treatment option to prepare for RAI treatment in patients who have side effects or who do not respond adequately to ATDs. It is also a salvage therapy in thyroid storm. In a retrospective study in patients with Graves' disease, amiodarone-induced thyrotoxicosis, or toxic nodular goiter, therapeutic plasmapheresis significantly decreased free thyroid hormone levels. 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).

Pharmacologic Therapy

Antithyroid Medications

Thionamide Drugs

Two drugs within this category, methimazole and propylthiouracil, are approved for the treatment of hyperthyroidism in the United States. They are classified as thioureylenes (thionamides), which incorporate an N–C–S=N group into their ring structures. ATDs are treatment options for Graves' disease, toxic adenoma, and MNG. Only in Graves' disease are ATDs considered to be definitive therapy.

Mechanism of Action

Methimazole and propylthiouracil share several mechanisms to inhibit the biosynthesis of thyroid hormone. 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 TRAb titers and restoration of normal suppressor T-cell function. However, perchlorate (ClO_4^-)(C1O4−), which has a different mechanism of action, also decreases TRAbs, suggesting that normalization of the thyroid hormone level may itself improve the abnormal immune function. Propylthiouracil inhibits the peripheral conversion of T_4 to T_3. This effect is dose-related and occurs within hours of propylthiouracil administration. Methimazole does not have this effect. ATDs do not inactivate existing stored or circulating T_3 and T_4. 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 propylthiouracil and methimazole 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 propylthiouracil and less than 10% for methimazole. 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 propylthiouracil. Approximately 80% of propylthiouracil is bound to plasma albumin, whereas methimazole is not protein-bound. Methimazole readily crosses the placenta and appears in breast milk. Older studies suggested that propylthiouracil crosses the placental membranes only one-tenth as well as methimazole; however, these studies were done in the course of therapeutic abortion early in pregnancy. Newer studies show little difference between fetal concentrations of propylthiouracil and methimazole, and both are associated with elevated TSH in about 20% and low T_4 in about 7% of fetuses.

Dosing and Administration

Dosing is different for the two ATDs. Methimazole is available as 5 and 10 mg tablets and propylthiouracil as 50 mg tablets. Methimazole is approximately 10 to 20 times more potent than propylthiouracil. Initial therapy with methimazole is given in two or three divided doses totaling 30 to 60 mg/day. Propylthiouracil 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 methimazole and propylthiouracil are 120 and 1,500 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 methimazole and propylthiouracil 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. Remission is defined as normal thyroid function tests lasting 1 year after discontinuation of ATD therapy. 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 age 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 TRAb titers at baseline or a reduction with treatment. Accurate methods to predict remission or relapse after 12 months of ATD therapy are lacking; however, a new assay that has better specificity for the detection of antibodies that stimulate the TSH receptors without detecting coexistent blocking antibodies may be a useful predictor of remission of Graves' disease.

ATD courses longer than 12 to 24 months are more likely to achieve remission. 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 disappears within 5 years without TBII fluctuation or enlargement of the goiter. In another study in which patients were treated for their first episodes of Graves' hyperthyroidism, 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. A systematic review on remission rates in children with Graves' disease found increasingly higher remission rates the longer the treatment duration (range 1.5-2.5 years to 9 years). In summary, longer treatment was associated with greater efficacy and is generally well tolerated.

It is important that patients be followed indefinitely at intervals of every 6 to 12 months after remission occurs. If a relapse occurs, alternate therapy with RAI or surgery is preferred over a second course of ATDs; however, continued long-term low-dose methimazole can be considered. 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, referred to as "block-replacement," is not recommended because of the higher rates of side effects seen with the larger doses of ATDs needed for this regimen.

Treatment of subclinical hyperthyroidism with ATDs or other therapies is patient-dependent. Subclinical hyperthyroidism is associated with an increased risk of cardiovascular morbidity (atrial fibrillation and heart failure) and may be associated with increased all-cause mortality. There is also an increased risk of hip fractures in postmenopausal women with subclinical hyperthyroidism. Most practitioners agree that the treatment of patients aged 65 years and older with TSH values persistently 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.

Adverse Effects

Minor adverse reactions to methimazole and propylthiouracil have an overall incidence of 5% to 25% depending on the dose and the drug, whereas major adverse effects occur in less than 5% of patients receiving these drugs. 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. Other options for persistent minor cutaneous reactions include switching to the other ATD or changing treatment modalities to RAI or surgery.

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 thionamide may be tried, but cross-sensitivity occurs for about 50% of patients.

Agranulocytosis is one of the serious adverse effects of ATD therapy and is characterized by fever, malaise, gingivitis, oropharyngeal infection, and a granulocyte count less than 200 to 500/mm^3 (0.2×10^9/L to 0.5×10^9/L). 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 thionamides, and the incidence varies from 0.5% to 6%. It is a dose-related adverse effect with methimazole but dose-independent for propylthiouracil. Certain HLA genotypes are associated with ATD-induced agranulocytosis, although routine testing is not currently recommended.

Prompt identification and treatment of agranulocytosis is key. The condition usually develops in the first 3 months of therapy. Because the onset is sudden, routine WBC count monitoring has not been recommended. Peripheral lymphocytes obtained from patients with propylthiouracil-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 methimazole 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 develop. Treatment of agranulocytosis

requires immediate suspension of the ATD and initiation of broad-spectrum antibiotics. 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. Definitive treatment of hyperthyroidism is subsequently required. Clinicians will often concomitantly provide an order for a complete blood cell count (with WBC count differential) when prescribing methimazole or propylthiouracil 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. 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 thionamide drug should not be converted to the alternate drug because of cross-sensitivity.

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. Registry data from Denmark found that ongoing use of methimazole was associated with an increase in the risk of being admitted to the hospital for acute pancreatitis, whereas propylthiouracil was not associated with an increased risk. This is a rare but serious side effect that patients should be made aware of.

Hepatotoxicity can be seen with both methimazole and propylthiouracil, 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. Labs usually reveal a cholestatic process with methimazole and a hepatocellular injury with propylthiouracil. Propylthiouracil-induced subclinical liver injury is common and is usually transient and asymptomatic. Thus, it has generally been thought that therapy with propylthiouracil may be continued with caution in the absence of symptoms and hyperbilirubinemia. However, cases of severe hepatic failure leading to death or the need for liver transplant do exist. The risk is relatively greater in children than adults. The risk appears to be dose-related in children and is associated with therapy lasting more than 4 months in duration. Thus, the American Thyroid Association (ATA) and the United States Food and Drug Administration (FDA) recommend against the use of propylthiouracil as first-line therapy in either adults or children. One of three exceptions includes the first trimester of pregnancy, when the risk of methimazole-induced embryopathy may exceed that of propylthiouracil-induced hepatotoxicity. Other exceptions include intolerance to methimazole and thyroid storm. Monitoring of serum transaminases is not explicitly recommended but baseline serum transaminases more than 5 times the upper limit of normal is a relative contradiction for initiating ATD therapy.

Several serious congenital malformations, including tracheoesophageal fistulas and choanal atresia, have been observed with methimazole use during pregnancy. Propylthiouracil has traditionally been considered the drug of choice throughout pregnancy for women with hyperthyroidism because of concerns about the possible teratogenic effects of methimazole. However, currently heightened concerns about the greater risk of hepatotoxicity with propylthiouracil when compared to methimazole have led to the recommendation that propylthiouracil no longer be considered a first-line drug, except during the first trimester of pregnancy. The choice of ATD during pregnancy has been further complicated by studies that suggest that fetuses exposed to either methimazole or propylthiouracil during gestation may increase the risk of drug-induced fetal malformations. The birth defects associated with propylthiouracil appear to be less severe than with methimazole, making propylthiouracil the preferred agent during the first trimester. Discussions surrounding this risk should be prioritized by the clinician caring for women of childbearing age or those planning to become pregnant. Women taking ATDs should contact their provider immediately if they become pregnant.

Recommendations regarding the management of thyroid disease during pregnancy include using the lowest effective dose of the ATD possible, targeting maternal serum FT_4/total T_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.

Radioactive Iodine

6 Although other radioisotopes have been used to ablate thyroid tissue, sodium iodide-131 (^{131}I) is considered to be the agent of choice for Graves' disease, toxic autonomous nodules, and toxic MNGs. 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 the 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. Lactating women and those planning to become pregnant within 6 months of RAI administration should also avoid RAI treatment. The curative nature of RAI treatment in Graves' disease makes it a desirable option for those who are candidates for it.

Several medications may be given with or surrounding the administration of RAI. 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 1 week 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 older adults are often treated with methimazole prior to RAI ablation. Pretreatment with propylthiouracil may lead to higher rates of treatment failure, but this does not appear to be the case with methimazole pretreatment. For patients with underlying cardiac disease, it may be necessary to reinstitute ATD therapy following RAI ablation. It is recommended to withdraw the thionamide 2 to 3 days prior to RAI treatment and to reinstitute it 3 to 7 days after therapy is concluded. Administering ATD immediately following RAI treatment may result in a higher rate of posttreatment recurrence or persistent hyperthyroidism. Studies done outside of the United States have shown that pretreatment with 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. Lithium is likely to achieve these effects by increasing RAI retention in the thyroid and inhibiting thyroid hormone release from the gland. However, the clinical significance of this is likely low, and given lithium's narrow therapeutic index, it is not recommended in most cases.

Compared to ATDs or surgery, RAI is associated with new or worsening Graves' ophthalmopathy. Theoretically, if a shared thyroidal and orbital antigen is involved in the pathogenesis of Graves' ophthalmopathy, antigen released with RAI treatment could aggravate preexisting 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 teprotumumab have been assessed in randomized controlled trials. 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. The most commonly reported adverse events with teprotumumab were muscle spasms, nausea, and alopecia. Hyperglycemia and hearing loss are other common adverse effects that must be monitored.

Destruction of the gland attenuates the hyperthyroid state, and hypothyroidism is almost inevitable. The success in treating hyperthyroidism depends on the dose administered. It is advisable that a second dose of RAI be given 6 months after the first RAI treatment if the patient remains hyperthyroid. A common approach to Graves' hyperthyroidism is to administer a single dose of 5 to 15 mCi (185-555 MBq; 80-200 μCi/g of tissue [3.0-7.4 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. Thyroid glands estimated to weigh more than 80 g may require larger doses of RAI. 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 post-treatment.

Most patients eventually become hypothyroid following successful thyroid ablation. Biochemical monitoring of FT_4, total T_3, and TSH should be done every 4 to 6 weeks post-RAI therapy for 6 months. Normalization of thyroid function tests and clinical improvement may occur 4 to 8 weeks after treatment. As such, antiadrenergic therapy and ATDs should be tapered off. The transition to hypothyroidism occurs most commonly 2 to 6 months after treatment. Chronic thyroid hormone replacement with levothyroxine should be initiated when FT_4 levels fall below the reference range. TSH levels may remain below the reference range for months after hyperthyroidism resolves and should not be used to adjust levothyroxine doses.

Education to patients on precautions to take to avoid radiation exposure to others post-RAI treatment is essential. The ATA developed best practices for radiation safety (Table 100-7). Recommendations relate to travel, home, and work/school. The length of time patients should practice these safety precautions can vary from days to weeks and depends on the dose of RAI administered. The healthcare provider administering the RAI therapy should discuss these safety precautions with patients and offer an alternative therapy if they cannot be observed.

TABLE 100-7

Instructions to Reduce Exposure to Others After ^{131}I RAI Treatment

- Avoid public transportation
- Sleep in a separate bed (approximately 6 feet of separation) from others
- Maintain at least 6 feet of distance from children and pregnant women and at least 3 feet of distance from others
- Avoid kissing and physical contact with others
- Minimize time in public places where you may be close to others
- Do not share cups, utensils, towels, or washcloths with others
- Drink plenty of water
- Sit to urinate and wipe the toilet seat after use
- Delay return-to-work

^{131}I, radioactive I-131.

Table created based on information in: Sisson JC, Freitas J, McDougall IR, et al. Radiation safety in the treatment of patients with thyroid disease by radioiodine ^{131}I: practice recommendations of the American Thyroid Association. Thyroid 2011;21(4):335–46.

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 (useful preoperatively). 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 preexisting 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 Japanese studies and may be an alternative to those with mild disease who cannot tolerate ATDs and want to avoid RAI or surgery. 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 35 to 50 mg of iodide per drop or as Lugol's solution, which contains 6.25 mg of iodide per drop. The typical dose of SSKI is 3 to 10 drops daily (150-500 mg) in divided doses, diluted in water or juice. For Lugol's solution, typical doses are 5 to 7 drops (31.25-43.75 mg) three times daily also mixed in water or juice. 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 adverse effects of iodide therapy are hypersensitivity reactions (skin rashes, drug fever, rhinitis, and conjunctivitis), salivary gland swelling, stomach upset, diarrhea, nausea, and vomiting. "Iodism" (metallic taste, burning mouth and throat, sore teeth and gums, symptoms of a head cold, and sometimes stomach upset and diarrhea) can occur with prolonged treatment and higher doses.

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, other therapies are needed to achieve euthyroid in certain etiologies. Furthermore, β-blockers neither reduce TRAb nor prevent thyroid storm. Propranolol, nadolol, atenolol, and metoprolol partially block the conversion of T_4 to T_3, but this contribution to the overall therapeutic effect is small in magnitude.

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 (atenolol and metoprolol) 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 (propranolol only), and those with spontaneous hypoglycemia. β-Blockers may also prolong gestation and labor during pregnancy. If a β-blocker is necessary during pregnancy for symptom control, propranolol is preferred. Atenolol should be avoided during pregnancy and postpartum as its minimal protein-binding allows the drug to accumulate in breast milk. Other notable side effects include nausea, vomiting, fatigue, insomnia, light-headedness, and bradycardia. When therapy is no longer necessary, β-blockers should be slowly discontinued to prevent acute withdrawal and possibly incite a thyroid storm.

Antiadrenergic agents such as centrally acting sympatholytics and calcium channel antagonists may have some role in the symptomatic treatment of hyperthyroidism. Small studies show that diltiazem and verapamil are effective in controlling symptoms and heart rate in patients with thyrotoxicosis. 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. Both medications reduced heart rate and improved hyperthyroid symptoms. While evidence is minimal, these alternatives can be used in patients with contraindications to β-blocking medications or in combination if symptoms are severe.

Special Populations

Graves' Disease and Pregnancy

Normal pregnancy is associated with alterations in the physiology of the thyroid gland, owing mostly to increased production of hCG. Thyroid hormone production is increased, and TSH levels are suppressed. Reference ranges for thyroid function tests are different in patients who are pregnant compared to nonpregnant individuals and vary according to trimester and population. Other effects include increased renal iodine excretion and increased thyroxine-binding proteins. A healthy, functioning thyroid gland will adapt to these changes and prevent overt hyperthyroidism. Many prenatal multivitamins also contain the recommended amount of iodine to account for this physiologic change. Gestational transient thyrotoxicosis (hCG-mediated transient TSH suppression) may occur during the first trimester. It is usually asymptomatic, and treatment with ATDs is not recommended. Differentiation between that and true hyperthyroidism relies on medical history, physical examination, and biochemical markers. RAIU scan should not be performed in pregnancy.

A very comprehensive guideline has been published by the ATA regarding the management of thyroid disease during pregnancy. 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 TRAb 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), ATD therapy is the treatment of choice for hyperthyroidism. Methimazole and propylthiouracil both cross the placenta and appear in breast milk. Methimazole is the preferred ATD in nursing patients due to the hepatotoxicity risk with propylthiouracil.

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. During this period, the risk of methimazole-associated embryopathy is believed to outweigh that of propylthiouracil-associated hepatotoxicity. To prevent fetal goiter and suppression of fetal thyroid function, propylthiouracil is usually prescribed in daily doses of 300 mg or less and tapered to 50 to 150 mg daily after 4 to 6 weeks. Propylthiouracil 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, methimazole has been thought to be the drug of choice because of the greater risk of hepatotoxicity with propylthiouracil. However, it is unclear whether this strategy of switching thionamides, and thus exposing the fetus to both drugs, is the optimum approach. If the switch is made from propylthiouracil to methimazole after the first trimester, a dose ratio of approximately 20:1 (propylthiouracil:methimazole) in total daily dose should be used. Thionamide doses should be adjusted to maintain FT_4 within 10% of the upper normal limit of the nonpregnant reference range. During the last trimester, TRAbs 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 the placental transfer of TRAbs, which stimulates thyroid hormone production in utero and postpartum. This is likely if the maternal TRAb titers were quite high. The disease is usually expressed 7 to 10 days postpartum, and treatment with ATDs (propylthiouracil 5-10 mg/kg/day or methimazole 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 ATDs, and methimazole is the therapy of choice in the United States. Long-term follow-up studies suggest that this form of therapy is quite acceptable, with 25% of a cohort experiencing remission every 2 years. However, lasting remission occurs only in a minority of pediatrics patients with Graves' disease after at least 1 year of ATD therapy. If remission is not achieved with methimazole or relapse occurs, RAI or surgery should be tried. RAI is effective but should be avoided in children under age 5 due to the risk of subsequent thyroid cancer. Thyroidectomy is also effective. It should be performed only by a high-volume surgeon to minimize complication risks.

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. 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. Diagnosis of thyroid storm is clinical, and several scoring systems have been developed to aid in prompt diagnosis. 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 100-8.

TABLE 100-8

Drug Dosages Used in the Management of Thyroid Storm

Drug	Regimen
Therapy Directed Against the Thyroid Gland	
Propylthiouracil	900-1,500 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)	5-8 drops every 6 hours in water or juice
Therapy Directed Against Peripheral Thyroid Hormone Effects	
Propranolol	60-120 mg orally every 6 hours
Esmolol	0.25-0.5 mg/kg IV push then 0.05-0.1 mg/kg/min continuous IV infusion
Therapy Directed Against Systemic Decompensation	
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

ATDs will block new hormone synthesis, while iodides will inhibit the release of preformed hormones. Propylthiouracil 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 methimazole 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 at least 1 hour 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.

Antiadrenergic therapy with β-blockers work to inhibit the effects of severe thyrotoxicosis. Propranolol is commonly used, while the short-acting agent esmolol is preferred in the intensive care unit, both because it may be used in patients 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. 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 FT_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 FT_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 and may be longer in pediatric patients. Therefore, if a thyrotoxic patient has his or her FT_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 the patient’s 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 the clinical and biochemical syndrome resulting from decreased thyroid hormone production. Biochemically, primary hypothyroidism is defined as TSH concentrations above the reference range and FT_4 and/or T_3 levels below the reference range. Clinically, hypothyroid symptoms affect multiple systems due to the pervasive actions of thyroid hormone.

EPIDEMIOLOGY—HYPOTHYROIDISM

The prevalence of hypothyroidism in the United States is estimated to be 9% to 11%, affecting women (76.1%) more than men (23.9%). The prevalence of hypothyroidism increases with age, with the highest risk (16%-17%) for those over 60 years old.

ETIOLOGY AND PATHOPHYSIOLOGY—HYPOTHYROIDISM

The etiologies of hypothyroidism can be categorized as primary, occurring at the level of the thyroid gland, secondary, occurring at the level of the pituitary, or tertiary, occurring at the level of the hypothalamus (Table 100-9). [7] The vast majority of patients have primary hypothyroidism due to thyroid gland failure caused by chronic autoimmune thyroiditis. Laboratory findings will show decreased levels of FT_4 and/or T_3 and increased levels of TSH as the hypothalamus and pituitary attempt to stimulate increased thyroid hormone production. Special populations with a 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.

TABLE 100-9

Causes of and Laboratory Findings in Hypothyroidism

	Primary Hypothyroidism	Central Hypothyroidism

Causes	• Hashimoto's disease
	• Iatrogenic hypothyroidism
	  ○ Medications
	  ○ Radioactive iodine treatment
	  ○ Surgical removal of thyroid tissue
	• Less common:
	  ○ Iodine deficiency
	  ○ Enzyme defects
	  ○ Thyroid hypoplasia
	  ○ Goitrogens
		• Pituitary disease
		  ○ Secreting or non-secreting tumors
		  ○ Sheehan's syndrome
		• Hypothalamic disease
		  ○ Trauma

Laboratory Findings	• FT_4 and/or T_3 below reference range • TSH above reference range	• FT_4 and/or T_3 below reference range • TSH within or below reference range

Central hypothyroidism, including secondary and tertiary hypothyroidism, is rare and affects both sexes equally. It is more often associated with pituitary than hypothalamic disorders but frequently involves both. Biochemically, central hypothyroidism is defined by low FT_4 and low or low-to-normal TSH concentrations. 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. Generalized (peripheral and central) resistance to thyroid hormone is extremely rare.

Chronic Autoimmune Thyroiditis

Chronic autoimmune thyroiditis (Hashimoto's disease) is the most common cause of spontaneous hypothyroidism in adults. In autoimmune thyroiditis, increased concentrations of antithyroid antibodies, TPOAbs and TgAbs, lead to thyroid tissue damage and decreased production of thyroid hormones. 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. TPOAbs are present in virtually all patients with Hashimoto's thyroiditis. These antibodies can fix complement and induce cytotoxic changes in thyroid cells. Patients may present either with a thyroid goiter and mild hypothyroidism or with thyroid gland atrophy and more severe thyroid hormone deficiency. Antibodies that stimulate 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 RAI 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. After partial thyroidectomy, the remaining tissue may or may not be able to compensate to maintain adequate thyroid hormone production. Excessive doses of ATDs 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 neurocognitive delay and/or growth impairment. 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 adults, hypothyroidism is rarely caused by iodine deficiency and goitrogens. But a lack of sufficient iodine to synthesize thyroid hormone is a potential cause of primary hypothyroidism in severe deficiency. Iodine overload can also block 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.

Pituitary Disease

TSH is required for normal thyroid secretion. Pituitary failure leads to thyroid atrophy and decreased thyroid secretion. 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. 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.

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 central hypothyroidism. In both adults and children, it may occur from cranial irradiation, trauma, infiltrative diseases, or neoplastic diseases.

CLINICAL PRESENTATION OF HYPOTHYROIDISM

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 adults, manifestations of hypothyroidism are nonspecific. In children, 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 neurodevelopmental delay and/or growth impairment. 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, lethargy and weakness.
- Symptoms of hypothyroidism present in multiple organ systems:

- Gastrointestinal: poor appetite, constipation, weight gain
- Nervous system: fatigue, low energy, sluggishness, lethargy, headache, impaired memory, decreased concentration, confusion, slowed speech
- Menstrual cycles: menorrhagia, infertility
- Musculoskeletal: weakness, muscle aches, cramps, stiffness, carpal tunnel syndrome
- Ear, nose, throat: hoarseness, impaired hearing

Signs

- Common signs of hypothyroidism include bradycardia, diminished reflexes, coarsening of skin and hair, puffiness of face and eyelids.
- Thyroid exam may be normal or may reveal goiter.
- The most severe presentation of hypothyroidism is myxedema coma.
- Signs of hypothyroidism are found in multiple organ systems:
  - Cardiac: bradycardia, hypertension, anemia, increased cholesterol and triglycerides, decreased cardiac output
  - Nervous system: cerebellar dysfunction
  - Face: periorbital puffiness, thickening of tongue
  - Extremities: peripheral edema, paresthesia, polyneuropathy, slow relaxation of deep tendon reflexes, proximal muscle weakness, slowed motor activity, increased creatinine kinase
  - Skin, nails, and hair: course, cold pale or dry skin, coarse, brittle or loss of hair, brittle nails

Diagnosis

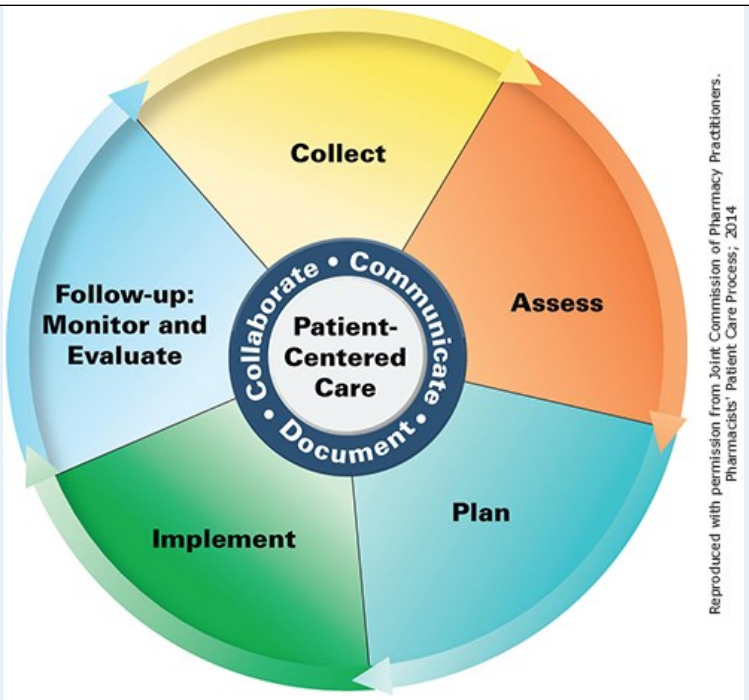
- Serum FT_4 and T_3 levels below reference range. Elevated serum TSH concentrations; in primary hypothyroidism TSH concentrations will increase before other markers.
- In central hypothyroidism, serum T_4 levels below reference range; serum TSH concentrations generally low or normal
- In subclinical hypothyroidism, serum free T_4 levels within the normal range; elevated serum TSH concentrations

Other Tests

- TPOAbs and TgAbs 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 personal or family history of thyroid or autoimmune disorders
- History of present illness including signs and symptoms: coarse skin and hair, cold or dry skin, periorbital puffiness, and bradycardia; cold intolerance, weight gain, constipation, weakness, muscle cramps, and myalgia (see Clinical Presentation Box)
- Current medications including over-the-counter and herbal medication use
- Objective data
  - Heart rate, BP, weight, and BMI
  - Labs (eg, TSH, FT_4, total T_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 100-9)
- 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 100-10)
- Monitoring parameters including efficacy (eg, resolution of signs and symptoms) and safety (arrhythmias, angina, osteoporosis, or

symptomatic hyperthyroidism), laboratory data (TSH, FT_4, total T_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 and interacting medications (see Table 100-12)
- Patient adherence to treatment plan using multiple sources of information
- Follow-up laboratory monitoring

****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.

The primary target for biochemical normalization is a TSH within the normal range. There is clinical debate over the optimal upper limit of the normal TSH range. Some clinicians advocate that the reference range should be modified from approximately 0.5 to 4.5 mIU/L to 0.5 to 3.5 mIU/L or even 0.5 to 2.5 mIU/L. If this premise is accepted, both the TSH values that trigger levothyroxine 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 hormones who would not necessarily benefit from such treatment. Those who favor narrowing the reference range proport that the upper end of the current range includes a proportion of patients with undiagnosed thyroid disease and that additional patients would, in fact, derive benefit from thyroid hormone treatment. There are calls by some for increasing the thyrotropin reference range specifically among individuals aged 80 years and older. TSH reference ranges also differ for different populations, such as those who are pregnant, specific ethnic groups, and older individuals.

General Approach to Treatment

Levothyroxine (L-thyroxine, T_4) is considered the drug of choice for treatment of hypothyroidism (Table 100-10). Other thyroid preparations exist but are not considered preferred therapy. Available thyroid preparations are synthetic (L-thyroxine, liothyronine) or natural in origin (ie, desiccated thyroid). They include either only T_4 (levothyroxine), only T_3 (liothyronine) or a combination of T_4 and T_3 (desiccated thyroid). Additional products containing combined T_4 and T_3, including thyroglobulin (Proloid) and liotrix (Thyrolar), have been voluntarily withdrawn from the US market.

TABLE 100-10

Thyroid Preparations Used in the Treatment of Hypothyroidism

Drug (Brand Name)	Dosage Form	Content	Relative Dose	Comments/Equivalency
Thyroid USP (Armour Thyroid, Adthyza, Nature-Throid, NP Thyroid, Westhroid, WP Thyroid) T_4:T_3 ratio approximately 4.2:1	Doses include 1/4, 1/2, 1, 1 ½, 2, 3, 4, and 5 grain tablets Armour Thyroid and NP Thyroid 1 grain = 60 mg; Nature-Throid, Westhroid, and WP Thyroid 1 grain = 65 mg	Desiccated pork thyroid gland	1 grain (equivalent to 74-100 mcg of T_4)	High T_3:T_4 ratio; inexpensive; Generic brands may not be bioequivalent
Levothyroxine (Ermeza, Euthyrox, Levoxyl, Synthroid, Thyquidity, Tirosint, Tirosint-SOL, Unithroid)	Tablets (eg, Euthyrox, Levoxyl, Synthroid, Unithroid): 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, 200, 300 mcg tablets Liquid-filled oral capsules (eg, Tirosint): 13-2000 mcg Liquid solution (eg, Ermeza, Thyquidity, Tirosint-Sol): 13, 20, 25, 30, 37.5, 44, 50, 62.5, 75, 88, 100, 112, 125, 137, 150, 175, and 200 mcg/mL Intravenous solution: 20, 40, 100 mcg/mL Intravenous powder for reconstitution: 100, 200, 500 mcg	Synthetic T_4	100 mcg	Stable; predictable potency; available oral tablet, oral capsule, oral solution, intravenous solution, and intravenous powder for solution; generics may be bioequivalent; when switching from natural thyroid to L-thyroxine, lower dose by one-half grain; variable absorption between products; daily dosing (half-life = 7 days); considered to be drug of choice
Liothyronine (Cytomel)	Tablets: 5, 25, and 50 mcg tablets Intravenous solution: 0.01 mg/mL	Synthetic T_3	33 mcg (~equivalent to 100 mcg T_4)	Uniform absorption, rapid onset; half-life = 1.5 days, rapid peak and troughs

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. 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 (Table 100-11).

TABLE 100-11

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 in primary hypothyroidism?	Levothyroxine replacement therapy has three main goals. These are (i) to provide resolution of the patients' symptoms and hypothyroid signs, (ii) to achieve normalization of serum thyrotropin, and (iii) to avoid overtreatment.	Strong 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	Although short-term outcome data in hypothyroid patients suggest that thrice-daily synthetic liothyronine may be associated with beneficial effects	Strong recommendation,

liothyronine or as sustained release triiodothyronine, that support the use of triiodothyronine therapy alone for the treatment of hypothyroidism?	on parameters such as weight and lipids, longer-term controlled clinical trials are needed before considering synthetic liothyronine therapy for routine clinical use.	moderate quality

Data from Jonklass J, Bianco AC, Bauer AJ, et al. Guidelines for the treatment of hypothyroidism: prepared by the American Thyroid Association Task Force on Thyroid Hormone Replacement. Thyroid 2014;24L:1670–1751. DOI:10.1089/thy.2014.0028. Stro ng recommendation: Benefits clearly outweigh risks and burden, or risks and burden clearly outweigh benefits. Weak recommendation: Benefits closely balanced with risks and burden. Quality of evidence: High, moderate, or low.

Pharmacologic Therapy

8 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 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. Animal studies suggest a higher T4:T3 ratio in rats treated with levothyroxine monotherapy compared to those treated with slow-release T_3 pellets. Evidence of the clinical effects of such treatment in humans is not available. If used, T_3 must be administered three times a day to achieve stable hormone concentrations. Dose titration to achieve stable euthyroidism may take longer than with levothyroxine.

9 The use of combination therapy of levothyroxine and liothyronine remains highly controversial, with conflicting results from clinical trials. Limited human data on T_4/T_3 combination therapy does not support improvement in biochemical parameters or quality of life. Though additional data in specific sub-populations is needed. 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.

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). This represents a 4:1 T_4 to T_3 ratio, compared to a 11-13:1 ratio produced endogenously in normally functioning thyroid glands. This is a relatively high proportion of T_3 and may cause thyrotoxicosis. As desiccated thyroid is an animal protein-derived product, there is a potential for allergies or the development of antibodies against the product. 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 FT_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 clear that T_4 is too insensitive as a measure of bioequivalency. 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. To avoid overtreatment and undertreatment, once a product is selected, switches between levothyroxine products in patients who are stable are not recommended.

Adverse Effects

Serious adverse effects are unusual if dosing is appropriate and euthyroid levels are maintained. However, over-replacement can lead to symptoms and consequences of hyperthyroidism. Specifically, monitoring of cardiovascular and osteoporotic effects of excess thyroid hormone levels is prudent. 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 the thyroid hormone tablet.

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. 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.

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. The risk for this complication seems to be related to the dose of levothyroxine and the patient's age and sex. 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 levothyroxine. 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 levothyroxine to achieve a normal TSH has no adverse effect on bone density.

Drug-Drug and Drug-Food Interactions

Levothyroxine has multiple interactions with foods, herbal products and other medications. Interactions that reduce levothyroxine absorption, reduce endogenous thyroid hormone production, increase T_4 metabolism, increase binding proteins, or block conversion of T_4 to T_3 increase the dose of levothyroxine replacement therapy needed. Conversely, interactions that increase levothyroxine absorption, decrease protein binding, or include thyroid activity decrease the levothyroxine replacement dosing requirements. Levothyroxine can also affect the dosing requirements of other narrow-therapeutic index medications including blood thinners, digoxin, insulin, seizure medications, and anesthesia (Table 100-12).

TABLE 100-12

Examples of Levothyroxine Drug, Food, Herbal Product, and Disease State Interactions

Interactions That Increase Levothyroxine Requirements	
Reduce levothyroxine absorption	Food/supplements ○ Iron ○ Calcium ○ Soy ○ Fiber ○ Coffee (Espresso) Over-the-counter ○ Aluminum antacids ○ Simethicone (GasX) ○ Orlistat (Alli, Xenical) Heavy metals ○ Chromium ○ Colloidal silver

	Phosphate binders ○ Sevelamer (Renagel) ○ Lanthanum (Fosrenol) Histamine blockers ○ Cimetidine (Tagamet) ○ Famotidine (Pepcid, Zantac) ○ Nizatidine (Axid) Proton pump inhibitors ○ Lansoprazole (Prevacid) ○ Omeprazole (Prilosec) ○ Esomeprazole (Nexium) ○ Dexlansoprazole (Dexilant, Kapidex) ○ Pantoprazole (Protonix) ○ Rabeprazole (Aciphex) Bile acid sequestrants ○ Cholestyramine (Questran) ○ Colesevelam (Welchol) ○ Colestipol (Colestid) Other ○ Sodium polystyrene sulfonate (Kayexalate) ○ Sucralfate (Carafate) ○ Raloxifene (Evista) Many herbal products also decrease levothyroxine absorption
Reduce thyroid hormone production	• Lithium • Amiodarone (Cordarone) • Iodine-containing medications • Laminaria (herbal) • Kelp
Increase T_4 metabolism	• Diabetes drugs • Antiseizure drugs (phenytoin, fosphenytoin, phenobarbital, carbamazepine) • Warfarin • Simvastatin • Others (rifampin, rifapentine, imatinib, lopinavir/ritonavir, chloroquine)
Increase binding proteins	High estrogen states ○ Oral contraceptives ○ Pregnancy ○ Postmenopausal hormone replacement
Block conversion of T_4 to T_3	• Amiodarone • β-Blockers • Selenium deficiency • Bugleweed (herbal)

Interactions That Decrease Levothyroxine Requirements	
Increase absorption	• European mandrake (herbal)
Decrease protein binding	• Age • Liver disease (cirrhosis) • Kidney disease (nephrosis) • Protein-losing enteropathies
Have thyroid activity	• Tiratricol (herbal) • Tyrosine (herbal) • Bugleweed (herbal) • Balm leaf (herbal) • Wild thyme (herbal)
Interactions That Affect the Dosing of Other Medications	
Levothyroxine may affect how other medications work in the body	• Anticoagulants (warfarin, apixaban, rivaroxaban) • Digoxin • Insulin • Antiseizure drugs • Anesthesia

The time to maximal absorption of levothyroxine is about 2 hours, and this should be considered when T_4 concentrations are determined. Ingestion of levothyroxine with food can impair its absorption. 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. 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.

Data suggest 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 can occur with tablet preparations. 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 to administer crushed tablets. The former procedure was found to be more convenient by providers. The timing of doses related to meals may be less problematic with liquid formulations of levothyroxine due to improved absorption when compared to tablets in patients taking proton pump inhibitors. Patients with gastritis appear to have lower dosing requirements with levothyroxine gel capsules compared to tablets. 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, these levothyroxine formulations may prove very convenient for patients. Studies in adults with hypothyroidism have found similar efficacy when levothyroxine is dosed at bedtime versus early morning.

Dosing and Administration

The average maintenance dose of levothyroxine for most adults is about 125 mcg/day. The replacement dose of levothyroxine is affected by body weight, age, comorbidities, and duration of hypothyroidism. Estimates of weight-based doses for replacement in hypothyroid patients without any

autonomous thyroid function are 1.6 to 1.7 mcg/kg/day, though hypothyroid patients still producing some thyroid hormone will require lower doses. The dose requirement may be better estimated based on ideal body weight rather than actual body weight. There is a wide range of replacement doses, necessitating individualized therapy and appropriate TSH monitoring to determine an adequate but not excessive dose. For patients unable to take levothyroxine orally, an intravenous preparation is available and should be initiated at 75% of the oral dose.

The ATA guidelines discuss two approaches to selecting initial treatment doses. The first approach is to initiate the estimated full maintenance dose. The second approach is to start at a lower dose and titrate to clinical effect. The benefit of the first approach is a shorter time to therapeutic dosing and quicker resolution of symptoms. Though the risks include over-repletion, which can lead to symptoms and sequelae of hyperthyroidism, most significantly cardiac manifestations.

Initiation of the estimated full maintenance dose is most appropriate for young and middle-aged patients without significant comorbidities and those with iatrogenic causes of hypothyroidism. In patients with long-standing disease and older individuals without known cardiac disease, therapy should be initiated with 50 mcg daily of levothyroxine. The recommended initial daily dose for older patients with known cardiac disease is 25 mcg daily.

It takes approximately 5 to 6 half-lives for TSH and FT_4 to achieve steady state after therapy initiation. While plasma TSH concentrations begin to fall within hours and are usually normalized within 2 weeks, it may take up to 6 weeks for some patients to see therapeutic effects. Therefore, monitoring more frequently than every 4 to 6 weeks does not provide a clinical advantage. TSH levels should be monitored every 4 to 6 weeks, and levothyroxine doses titrated in increments of 12.5 to 25 mcg until TSH levels within the normal range are achieved.

Once euthyroidism is attained, the daily maintenance dose of levothyroxine does not fluctuate greatly. As patients age, the dosing requirement may need to be reduced. TSH should continue to be monitored yearly once therapeutic dosing is established, and more often if significant changes in medications, diet or supplement use, changes among brand or generic products occur, symptoms develop, or poor absorption is suspected. 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.

10 TSH and T_4 concentrations are used to monitor therapy. The TSH concentration is the most sensitive and specific monitoring parameter for adjustment of levothyroxine dose. Third-generation TSH assays improved the accuracy with which thyroid hormone replacement can be monitored. 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. Serum T_4 concentrations can be useful in detecting noncompliance, malabsorption, or changes in levothyroxine product bioequivalence, among other things. 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, several antiseizure medications (phenobarbital, phenytoin, and carbamazepine), and rifampin. 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 FT_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 levothyroxine. Keeping FT_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.

TSH-suppressive levothyroxine therapy is used in patients with papillary or follicular thyroid cancer to reduce TSH levels and minimize the growth and function of abnormal thyroid tissue. It can also be given to patients with nodular thyroid disease and diffuse goiter, and to patients with a history of thyroid irradiation. 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 select 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. Levothyroxine 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, sex, 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.

Special Populations

Subclinical Hypothyroidism

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 may present with 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 their nonspecific nature. 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. The risk of progression is significantly greater in individuals with TPOAbs 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 aged 80 years or older with subclinical hypothyroidism. These results argue against the routine use of levothyroxine for the treatment of subclinical hypothyroidism, particularly in older adults. 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. While most patients with subclinical hypothyroidism can be observed without treatment, treatment may be indicated for patients with subclinical hypothyroidism and TSH levels of 10 mU/L or higher, or for young and middle-aged individuals with subclinical hypothyroidism and symptoms consistent with mild hypothyroidism.

Myxedema Coma

Myxedema coma is a rare consequence of decompensated hypothyroidism. Clinical features include hypothermia, advanced stages of hypothyroid symptoms, and altered sensorium ranging from delirium to coma. Any underlying disorder that may have precipitated the event, such as sepsis or myocardial infarction, must be diagnosed and treated. 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 treatment with IV 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. Supportive therapy must be instituted to maintain adequate ventilation, BP, and body temperature and ensure euglycemia. 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.

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 intelligence quotient (IQ) scores. 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

During pregnancy, thyroid hormone production increases, the thyroid gland increases in size, the daily iodine requirement increases, thyroxine-binding protein concentrations increase, and there is increased degradation of T_4 by placental deiodinase enzymes. The recommended dietary iodine allowance is higher (250 mcg/day) for patients who are pregnant or breastfeeding than for nonpregnant adults. hCG stimulates thyroid hormone secretion, which can lead to decreased concentrations of TSH. These changes can lead to new diagnoses of overt maternal hypothyroidism in patients euthyroid before conception. For patients treated with levothyroxine before pregnancy, 50% to 85% require dose increases during pregnancy. Untreated hypothyroidism during pregnancy can lead to premature birth, low birth weight, pregnancy loss, and impaired fetal neurocognitive development, so prompt diagnosis and treatment are necessary. As TSH levels and binding protein concentrations are altered during pregnancy, population-based trimester-specific reference ranges are used for diagnosis and monitoring. Screening is recommended at the time of pregnancy and every 4 weeks through mid-pregnancy in patients euthyroid at baseline. For patients treated with levothyroxine prior to pregnancy, a dose increase of 25% to 30% (two extra tablets) is recommended as soon as pregnancy is suspected. Levothyroxine is the drug of choice for hypothyroidism during pregnancy. Treatment can be discontinued for patients diagnosed during pregnancy and decreased to pre-pregnancy doses for patients previously treated with levothyroxine after delivery with repeat TSH monitoring 6 weeks postpartum.

EVALUATION OF THERAPEUTIC OUTCOMES—HYPOTHYROIDISM

Patients with idiopathic hypothyroidism and Hashimoto's thyroiditis on optimal thyroid hormone replacement therapy should have TSH and FT_4 serum concentrations in the normal range. 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. 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), although it may take several months for the full benefit of therapy to manifest. Many subjective symptoms of hypothyroidism are nonspecific and may be due to other causes. Therefore, symptoms should be assessed in the context of biochemical parameters.

CONCLUSION

Hypothyroidism is a common disorder but if 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.

ACKNOWLEDGMENTS

Michael P. Kane and Gary Bakst are acknowledged for authoring this chapter in previous editions and whose work was extensively used in this revised chapter.

KEY RESOURCES

KEY RESOURCES

General Physiology and Hormone Regulation

Carvalho DP, Dupuy C. Thyroid hormone biosynthesis and release. Mol Cell Endocrinol 2017;458:6–15. DOI:10.1016/j.mce.2017.01.038.

Review of physiology involved in thyroid hormone biosynthesis. Provides additional detail on the normal functioning of the thyroid gland.

Hyperthyroidism

Ross DS, Burch HB, Cooper DS, et al. 2016 American Thyroid Association Guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. Thyroid 2016;26:1343–421. DOI:10.1089/thy.2016.0229.

ATA guidelines for the diagnosis and management of hyperthyroidism and thyrotoxicosis. Structured as 24 questions and 124 recommendations, some with multiple parts, to guide assessment, diagnosis, pharmacotherapy selection, dosing, administration, and monitoring. Includes tables and figures that highlight and summarize clinically important information.

Smith TJ, Hegedüs L. Graves' disease. N Engl J Med 2016;375:1552–65. DOI:10.1056/NEJMra1510030.

Review article discussing epidemiology, clinical presentation, pathogenesis, diagnosis, and therapy for Graves' disease. Provides tables summarizing treatment options for Graves' disease and thyroid-associated ophthalmopathy.

Hypothyroidism

Jonklass J, Bianco AC, Bauer AJ, et al. Guidelines for the treatment of hypothyroidism: prepared by the American Thyroid Association Task Force on Thyroid Hormone Replacement. Thyroid 2014;24:1670–751. DOI:10.1089/thy.2014.0028.

American Thyroid Association (ATA) guidelines for treatment of hypothyroidism. Structured as 24 questions, some with multiple parts, to guide pharmacotherapy selection, dosing, administration, and monitoring. The guideline is divided into four sections: levothyroxine therapy, therapies other than levothyroxine alone, hospitalized patients, and use of thyroid hormone analogs.

Chaker L, Bianco AC, Jonklaas J, et al. Hypothyroidism. Lancet 2017;390:1550–62. DOI:10.1016/S0140-6736(17)30703-1.

Review article discussing epidemiology, risk factors, causes, clinical presentation, diagnosis, and treatment of hypothyroidism. Provides a succinct summary of key clinical topics.

Pregnancy and Postpartum

Alexander EK, Pearce EN, Brent GA, et al. 2017 guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. Thyroid 2017;27(3):315–89. DOI:10.1089/thy.2016.0457.

ATA guidelines for the diagnosis and management of thyroid diseases during pregnancy and postpartum. Structured as 111 questions and 97 recommendations to guide testing and screening, nutrition related to thyroid disease, epidemiology, management of thyroid disorders in pregnancy, lactation, and postpartum, as well as fetal and neonatal considerations. These guidelines also include future research directions.

ABBREVIATIONS

ATA	American Thyroid Association
ATD	antithyroid drug
AUC	area under the curve

BMI	body mass index
BP	blood pressure
cGy	centigray
C_{max}	maximum concentration
(ClO_4^-)(C1O4−)	perchlorate
DIT	diiodotyrosine
FDA	United States Food and Drug Administration
FSH	follicle-stimulating hormone
FT_3	free triiodothyronine
FT_4	free thyroxine
H_2O_2	hydrogen peroxide
hCG	human chorionic gonadotropin
HLA	human leukocyte antigen
I^-	iodide
^{131}I	radioactive iodine; sodium iodide-131
L-thyroxine	levothyroxine
LH	luteinizing hormone
MIT	monoiodotyrosine
MNG	multinodular goiter
NIS	Na^+/I^- symporter
PRTH	pituitary resistance to thyroid hormone
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
TcO_4^- TcO4−	pertechnetate
TG	thyroglobulin
TgAb	thyroglobulin antibody
TPO	thyroid peroxidase
TPOAb	thyroid peroxidase antibodies
TR	thyroid hormone receptor
TRAb	thyrotropin receptor antibody
TRH	thyrotropin-releasing hormone
TRIAC	triiodothyroacetic acid
TSH	thyroid-stimulating hormone
WBC	white blood cell

BIBLIOGRAPHY

Alexander EK, Pearce EN, Brent GA, et al. 2017 guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. Thyroid 2017;27(3):315–89. DOI: 10.1089/thy.2016.0457.

Azizi F, Amouzegar A, Tohidi M, et al. Increased remission rates after long-term methimazole therapy in patients with Graves' disease: results of a randomized clinical trial. Thyroid 2019;29:1192–1200. DOI: 10.1089/thy.2019.0180.

Bandai S, Okamura K, Fujikawa M, et al. The long-term follow-up of patients with thionamide-treated Graves' hyperthyroidism. Endocrine J 2019;66:535–45. DOI: 10.1507/endocrj.EJ18-0418.

Barbesino G. Misdiagnosis of Graves' disease with apparent severe hyperthyroidism in a patient taking biotin megadoses. Thyroid 2016;26:860–63. DOI: 10.1089/thy.2015.0664.

Beck-Peccoz P, Giavoli C, Lania A. A 2019 update on TSH-secreting pituitary adenomas. Endocrinol Invest 2019;42(12):1401–6. DOI: 10.1007/s40618-019-01066-x.

Benvenga S, Carlé A. Levothyroxine formulations: pharmacological and clinical implications of generic substitution. Adv Ther 2019;36(Suppl 2):S59–71. DOI: 10.1007/s12325-019-01079-1.

Biondi B, Cappola AR, Cooper DS. Subclinical hypothyroidism: a review. JAMA 2019;322(2):153–60. DOI: 10.1001/jama.2019.9052.

Brix TH, Lund LC, Henriksen DP, et al. Methimazole and risk of acute pancreatitis. Lancet Diabetes Endocrinol 2020;8:187–89. DOI: 10.1016/S2213-8587(20)30025-5.

Burch HB, Cooper DS. Management of Graves' disease: a review. JAMA 2015;314:2544–54. DOI: 10.1001/jama.2015.16535.

Cappola AR. The thyrotropin reference range should be changed in older patients. JAMA 2019;322(20):61–2. DOI: 10.1001/jama.2019.14728.

Carvalho DP, Dupuy C. Thyroid hormone biosynthesis and release. Molecular and Cellular Endocrinology 2017;458:6–15. DOI: 10.1016/j.mce.2017.01.038.

Chaker L, Bianco AC, Jonklaas J, et al. Hypothyroidism. Lancet 2017;390(10101):1550–62. DOI: 10.1016/S0140-6736(17)30703-1.

Chen W-T, Chi CC. Associations of HLA genotypes with antithyroid drug-induced agranulocytosis: a systematic review and meta-analysis of pharmacogenomics studies. Br J Clin Pharmacol 2019;85:1878–87. DOI: 10.1111/bcp.13989.

Dosiou C, Kossler AL. Thyroid eye disease: navigating the new treatment landscape. J Endocrine Soc 2021;5:1–13. DOI: 10.1210/jendso/bvab034.

Douglas RS, Kahaly GJ, Patel A, et al. Teprotumumab for the treatment of active thyroid eye disease. N Engl J Med 2020;382:341–52. DOI: 10.1056/NEJMoa1910434.

Elston MS, Sehgal S, Du Toit S, et al. Factitious Graves' disease due to biotin immunoassay interference: a case and review of the literature. J Clin Endocrinol Metab 2016;101:3251–5. DOI: 10.1210/jc.2016-1971.

Esfandiari NH, Papaleontiou M. Biochemical testing in thyroid disorders. Endocrinol Metab Clin North Am 2017;46:631–48. DOI: 10.1016/j.ecl.2017.04.002.

Feller M, Snel M, Moutzouri E, et al. Association of thyroid hormone therapy with quality of life and thyroid-related symptoms in patients with subclinical hypothyroidism: a systematic review and meta-analysis. JAMA 2018;320:1349–59. DOI: 10.1001/jama.2018.13770.

Francis N, Francis T, Lazarus JH, et al. Current controversies in the management of Graves' hyperthyroidism. Expert Rev Endocrinol Metab 2020;15:159–69. DOI: 10.1080/17446651.2020.1754192.

Glinoer D, Cooper DS. The propylthiouracil dilemma. Curr Opin Endocrinol Diabetes Obes 2012;19(5):402–7. DOI: 10.1097/MED.0b013e3283565b49.

Goichot B, Caron P, Landron F, et al. Clinical presentation of hyperthyroidism in a large representative sample of outpatients in France: relationships with age, aetiology and hormonal parameters. Clin Endocrinol (Oxf) 2016;84:445–51. DOI: 10.1111/cen.12816.

Hammond EN, Vangu M-D-T HW. Effect of adjuvant lithium on thyroxine (T4) concentration after radioactive iodine therapy. Eur J Nucl Med Mol Imaging 2016;43:1980–7. DOI: 10.1007/s00259-016-3388-3.

Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association Management Guidelines for adult patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2016;26(1):1–133. DOI: 10.1089/thy.2015.0020.

Jonklaas J, Bianco AC, Bauer AJ, et al. Guidelines for the treatment of hypothyroidism: prepared by the American Thyroid Association task force on thyroid hormone replacement. Thyroid 2014;24:1670–1751. DOI: 10.1089/thy.2014.0028.

Jonklaas J, Bianco AC, Cappola AR, et al. Evidence-based use of levothyroxine/liothyronine combinations in treating hypothyroidism: a consensus document. Thyroid 2021;31(2):156–82. DOI: 10.1089/thy.2020.0720.

Kahaly GJ, Bartalena L, Hegedüs L, et al. 2018 European Thyroid Association Guideline for the management of Graves' hyperthyroidism. Eur Thyroid J 2018;7:167–86. DOI: 10.1159/00049038.

Kitahara CM, Berrington de Gonzalez A, Bouville A, et al. Association of radioactive iodine treatment with cancer mortality in patients with hyperthyroidism. JAMA Intern Med 2019;179:1034–42. DOI: 10.1001/jamainternmed.2019.0981.

Kitahara CM, Preston DL, Sosa JA, et al. Association of radioactive iodine, antithyroid drug, and surgical treatments with solid cancer mortality in patients with hyperthyroidism. JAMA Netw Open 2020;3(7):e209660. DOI: 10.1001/jamanetworkopen.2020.9660.

Mazhari A, Emanuele MA, Espiritu B. Desensitization to methimazole. Endocr Pract 2021;27(3):185–90. DOI: 10.1016/j.eprac.2020.10.019.

Mendoza A, Hollenberg AN. New insights into thyroid hormone action. Pharmacol Ther 2017;173:135–45. DOI: 10.1016/j.pharmthera.2017.02.012.

Mooijaart SP, Du Puy RS, Stott DJ, et al. Association between levothyroxine treatment and thyroid-related symptoms among adults aged 80 years and older with subclinical hypothyroidism. JAMA 2019;322(20):1977–86. DOI: 10.1001/jama.2019.17274.

Peters C, van Trotsenburg ASP, Schoenmakers N. Diagnosis of endocrine disease: congenital hypothyroidism: update and perspectives. Eur J Endocrinol 2018;179:R297–317. DOI: 10.1530/EJE-18-0383.

Ross DS, Burch HB, Cooper DS, et al. 2016 American Thyroid Association Guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. Thyroid 2016;26:1343–421. DOI: 10.1089/thy.2016.0229.

Simsir IY, Ozdemir M, Duman S, et al. Therapeutic plasmapheresis in thyrotoxic patients. Endocrine 2018;62(1):144–8. DOI: 10.1007/s12020-018-1661-x.

Smith TJ, Hegedüs L. Graves' disease. N Engl J Med 2016;375:1552–65. DOI: 10.1056/NEJMra1510030.

Thyroid disease: assessment and management. National Institute for Health and Care Excellence (NICE). Available at: https://www.nice.org.uk/guidance/ng145.

van Lieshout JM, Mooij CF, van Trotsenburg ASP, et al. Methimazole-induced remission rates in pediatric Graves' disease: a systematic review. Eur J Endocrinol 2021 Jun 1;EJE-21-0077.R1. DOI: 10.1530/EJE-21-0077.

Van Uytfanghe K, Ehrenkranz J, Halsall D, et al. Thyroid stimulating hormone and thyroid hormones (triiodothyronine and thyroxine): an American Thyroid Association- review of commissioned current clinical and laboratory status. Thyroid 2023;33(9):1013–28. DOI: 10.1089/thy.2023.0169.

Virili C, Trimboli P, Romanelli F, et al. Liquid and softgel levothyroxine use in clinical practice: state of the art. Endocrine 2016;54:3–14. DOI: 10.1007/s12020-016-1035-1.

Williams GR, Bassett JHD. Thyroid diseases and bone health. J Endocrinol Invest 2018;41:99–109. DOI: 10.1007/s40618-017-0753-4.

Wyne KL, Nair L, Schneiderman CP, et al. Hypothyroidism prevalence in the United States: a retrospective study combining National Health and Nutrition Examination Survey and claims data, 2009-2019. J Endocr Soc 2023;7:1–11. DOI: 10.1210/jendso/bvac172.

Ylli D, Klubo-Gwiezdzinska J, Wartofsky L. Thyroid emergencies. Pol Arch Intern Med 2019;129:526–34. DOI: 10.20452/pamw.14876.

Ylli D, Wartofsky L, Burman KD. Evaluation and treatment of amiodarone-induced thyroid disorders. J Clin Endocrinol Metab 2021;106:226–36. DOI: 10.1210/clinem/dgaa68.

SELF-ASSESSMENT QUESTIONS

1. Which best describes the role of thyroid peroxidase (TPO) in thyroid hormone synthesis?
   A. Catalyzes iodine oxidation
   B. Facilitates coupling reactions
   C. Stores iodine
   D. Transports iodine against an electrochemical gradient
2. Which statement comparing triiodothyronine (T_3) and thyroxine (T_4) is true?
   A. T_4 has 10-fold higher binding affinity for thyroid hormone receptors than T_3
   B. T_4 is 10-times more highly protein bound than T_3
   C. T_3 is produced in a fourfold higher concentration from the thyroid gland than T_4
   D. T_3 is four times more potent than T_4
3. Which patient should be recommended for total thyroidectomy based on their clinical presentation?
   A. 50-year-old male with multinodular goiter with large thyroid gland (80 g) having difficulty swallowing
   B. 33-year-old female with Graves' disease who is pregnant in her third trimester
   C. 10-year-old male with MNG who does not have access to a high-volume thyroid surgeon
   D. 85-year-old female with toxic adenoma and thyroid gland of 30 g who prefers the least invasive therapy
4. A patient with elevated radioactive iodine uptake (RAIU) scan and positive thyrotropin receptor antibodies (TRAbs) most likely has which cause of thyrotoxicosis?
   A. Graves' disease
   B. Multinodular goiter
   C. Painless thyroiditis
   D. Toxic adenoma
5. Which is the best therapy to manage Graves' disease in a patient during their first trimester of pregnancy?
   A. Total thyroidectomy
   B. Radioactive iodine
   C. Methimazole
   D. Propylthiouracil
6. Frank is a 70-year-old male with hyperthyroidism due to toxic multinodular goiter. His thyroid gland is 40 g and he is not experiencing any symptoms of his enlarged goiter such as difficulty swallowing. His goal is definitive therapy. Which is the best therapy for his management?

A. Total thyroidectomy

B. Radioactive iodine

C. Methimazole

D. Potassium iodide

7. Grant is a 46-year-old male with hyperthyroidism due to Graves' disease who is starting high dose methimazole therapy for management. Which counseling point about methimazole should he absolutely receive today?

A. Arthralgias are common and usually experienced within the first 6 months of therapy

B. Get regular testing of serum transaminases due to the risk of hepatotoxicity

C. Get a WBC count at the first sign of infection due to the risk of agranulocytosis

D. Development of a minor rash or itching contraindicates further trials of thionamides

8. Candace is a 36-year-old woman with newly diagnosed Graves' disease, who experiences insomnia, tremor, and palpitations. She has no significant medical history and is currently taking no medications. She is scheduled to receive radioactive iodine treatment in 1 week. Initiation of which medication is best to recommend to reduce her symptoms within hours?

A. Diltiazem

B. Propylthiouracil

C. Lugol's solution

D. Nadolol

9. Sonja is a 40-year-old woman with Graves' disease hospitalized for thyroid storm. Which should be given as initial therapy to block new thyroid hormone synthesis?

A. Prednisone

B. Lugol's solution

C. Propylthiouracil

D. Propranolol

10. What is the most appropriate initial dose of thyroid replacement therapy for a 70-year-old patient (weight: 114 kg, height: 5'10" [118 cm]) with hypothyroidism, coronary artery disease status post myocardial infarction 3 years ago, and peripheral arterial disease?

Armour Thyroid USP 60 mg po daily

Levothyroxine 175 mcg po daily

Liothyronine 25 mcg po daily

Synthroid 25 mcg po daily

11. What laboratory monitoring is recommended to assess the therapeutic effect of thyroid hormone replacement therapy?

A. Thyroid stimulatory hormone (TSH) every 2-3 weeks

B. Thyroid stimulating hormone (TSH) every 4-6 weeks

C. Free thyroxine (FT_4) every 2-3 weeks

D. Total thyroxine (TT_4) every 4-6 weeks

12. Which is true regarding the role of synthetic T_3 in the treatment of hypothyroidism?

A. Synthetic T_3 is the first-line treatment for hypothyroidism.

B. Synthetic T_3 has lower risk of adverse effects than synthetic T_4.

C. Additional research is needed before use of synthetic T_3 should be recommended.

D. Addition of synthetic T_3 should be recommended for patients with continued symptoms of hypothyroidism on synthetic T_4 monotherapy.

13. Which medication interacts with levothyroxine to block the conversion of T_4 to T_3?

A. Amiodarone

B. Calcium

C. Lithium

D. Tiratricol

14. Which counseling point should be included when educating a patient starting levothyroxine treatment?

A. Discontinue all calcium and iron containing supplements.

B. Take levothyroxine in the morning before breakfast.

C. Take levothyroxine two hours before or 30 minutes after meals.

D. Take with a full glass of water and remain upright for 30 minutes after administration of levothyroxine.

15. Which statement is true regarding levothyroxine dose adjustments in pregnant patients?

A. Most pregnant patients require decreased doses of levothyroxine due to increased peripheral deiodinase activity.

B. Most pregnant patients require decreased doses of levothyroxine due to increased T_4 production.

C. Most pregnant patients required increased doses of levothyroxine due to decreased volume of distribution.

D. Most pregnant patients require increased doses of levothyroxine due to increased production of binding proteins.

ANSWERS

1. **A.** Thyroid peroxidase is the key enzyme that catalyzes iodine oxidation to promote thyroid hormone synthesis (answer A is correct). Thyroglobulin (TG) is a large glycoprotein that stores iodine and facilitates the coupling reactions involved in thyroid hormone synthesis (answers B and C are incorrect). The Na+/I- symporter (NIS) actively transports iodine against an electrochemical gradient driven by the coupled transport of sodium (answer D is incorrect). See text in "Thyroid Hormone Synthesis."

2. **D.** T_3 is a four-times more potent than T_4 (answer D is correct), has a 10- to 15-fold higher binding affinity at thyroid hormone receptors than T_4

(answer A is incorrect), is produced in lower concentrations than T_4 (answer C is incorrect), and is more highly protein bound than T_4 (answer B is incorrect). The majority of circulating T_3 is produced by peripheral conversion from T_4 by deiodinase enzymes. See text in "Thyroid Hormone Regulation and Action."

3. **A.** Surgery is an option for many cases of thyrotoxicosis. In multinodular goiter, it is preferred over RAI in cases of cosmetic issues or pressure symptoms (answer A is correct). Thyroidectomy should only be considered in pregnancy when rapid control of hyperthyroidism is required and antithyroid drugs are not an option. It is best to avoid surgery during the first and third trimesters (answer B is incorrect). Hyperthyroidism in pediatric patients is preferably managed with thionamides. Thyroidectomy is an option but should only be performed by a high-volume surgeon to minimize complication risks (answer C is incorrect). Surgery is the most invasive option between it and RAI or ATDs (answer D is incorrect). See text in "Nonpharmacologic Therapy."

4. **A.** 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 (answers 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. Graves' disease is a cause of thyrotoxicosis associated with elevated RAIU that specifically develops antibodies to thyrotropic receptors and can be a specific test for diagnosis (answer A is correct). See text under "Causes of Thyrotoxicosis Associated with Elevated RAIU."

5. **D.** During pregnancy, ATDs are the treatment of choice for hyperthyroidism. RAI is contraindicated in pregnancy and during lactation (answer B is incorrect). Thyroidectomy is not recommended during pregnancy, especially during the first and third trimesters owing to the risks to the fetus (answer A is incorrect). Surgery should only be considered in pregnancy when rapid control of hyperthyroidism is required, and ATDs are not an option. Propylthiouracil is the thionamide of choice during the first trimester of pregnancy (answer D is correct). During this period, the risk of methimazole-associated teratogenic effects is more concerning than propylthiouracil-associated hepatotoxicity (answer C is incorrect). See text from section "Special Populations."

6. **B.** For patients with MNG, RAI or surgery are the preferred treatment options and only definitive therapies (answers C and D are incorrect). Iodide is contraindicated in toxic MNG as it provides more substrate for thyroid hormone synthesis (answer D is incorrect). Surgery is best for younger patients and those with large goiters creating symptoms (answer A is incorrect). For older patients, those with minimal mass-related symptoms, and toxic MNG, RAI is preferred (answer B is correct). See Table 100-6 and text under section "Pharmacologic Therapy."

7. **C.** Hepatotoxicity is an adverse effect that is more common and serious with propylthiouracil than methimazole. Monitoring of serum transaminases is not explicitly recommended while on thionamide therapy (answer B is incorrect). Agranulocytosis is a rare and serious adverse effect that usually develops in the first 3 months of therapy (answer C is correct). A differential WBC count should be obtained at the first sign of infection. It is a dose-related adverse effect with methimazole. Arthralgias are possible but not common and generally occur after 6 months of therapy (answer A is incorrect). Minor skin reactions such as rash or itching are possible and do not necessarily require discontinuation of the drug or absolute avoidance of thionamides in the future (answer D is incorrect). See text in section "Antithyroid Medications."

8. **D.** Several medications may be given with or surrounding RAI therapy, including antiadrenergic agents, ATDs, and iodides. It takes weeks for thioamides (answers B is incorrect) 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 is incorrect) 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 and have strong data to support their use (answer D is correct). Other antiadrenergic agents, such as calcium channel antagonists, have limited data for use in thyrotoxicosis and should only be considered in those with contraindications to β-blockers (answer A is incorrect). See text in section "Radioactive Iodine" under "Pharmacologic Therapy."

9. **C.** 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 100-8). ATDs will block new hormone synthesis by the thyroid gland (answer C is correct). Antiadrenergic therapy with β-blockers will inhibit the effects of

severe thyrotoxicosis (answer D is incorrect). Corticosteroids may be used, although the benefits derived from them are to treat and avoid system decompensation (answer A is incorrect). 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 (answer B is incorrect). See text in section "Thyroid Storm" under "Special Populations."

10. **D.** Levothyroxine is the drug of choice for the treatment of hypothyroidism. For patients who are elderly with cardiovascular disease, starting with a low dose and titrating to clinical effect is recommended to avoid adverse cardiac reactions with over-supplementation (answer D is correct). It may be appropriate to start at full therapeutic dosing, including weight-based dosing of 1.6 mg/kg/day, for younger patients or those without cardiovascular disease, but that would not be optimal in this case (answer B is incorrect). Desiccated thyroid products are not preferred due to the higher proportion of T3 in animal thyroid glands and the potential for allergy or antigenic response (answer A is incorrect). Similarly, synthetic T_3 products are not preferred due to multiple daily dosing, longer time to steady state, and higher risk of cardiovascular adverse effects (answer C is incorrect). See text in section "Hypothyroidism Pharmacologic Therapy."

11. **B.** Serum thyroid stimulating hormone (TSH) is the preferred monitoring for thyroid hormone replacement therapy as TSH responds more quickly to therapy than T_4. Due to the 7-day half-life of levothyroxine and the time needed to achieve steady state, it often takes 4 to 6 weeks to see the impact of dose initiation or adjustment (answer B is correct). Monitoring more frequently may not provide accurate information on current dosing effects (answer A is incorrect). Total T_4 is impacted significantly by protein is not the binding and most reliable laboratory parameter for measuring thyroid hormone levels (answer D is incorrect). Free T_4 has utility in assessing thyroid hormone replacement therapy, particularly in the setting of subclinical hypothyroidism and continued systems despite normalized TSH levels. However, TSH remains the preferred monitoring parameter in most settings (answer C is incorrect). See text in section "Evaluation of Therapeutic Outcomes—Hypothyroidism."

12. **C.** Both the 2014 ATA Guidelines on Treatment of Hypothyroidism and the 2021 ATA/BTA/ETA Consensus Document on Evidence-based use of levothyroxine/liothyronine combinations in treating hypothyroidism recommend against use of synthetic T_3 at this time due to a lack of evidence of clinical benefit (answer C is correct). These documents also outline specific research questions that should be pursued to elucidate the role of synthetic T_3 in the clinical management of hypothyroidism. Persistent hypothyroid symptoms despite levothyroxine therapy are the most common clinical scenario where synthetic T_3 is considered. However, the evidence does not support T_3 use, and the ATA guidelines specifically recommend against use in this case (answer D is incorrect). Synthetic T_4 (levothyroxine), not synthetic T_3, is the drug of choice for treatment of hypothyroidism. Some studies have shown an increased risk of cardiovascular side effects with use of T_3 (answer B is incorrect). See text in section "Hypothyroidism Pharmacologic Therapy."

13. **A.** Amiodarone interacts with levothyroxine through multiple mechanisms, including reducing thyroid hormone production and blocking the conversion of T_4 to T_3 (answer A is correct). Lithium interacts by reducing thyroid hormone production (answer C is incorrect). Calcium can interact by reducing levothyroxine absorption (answer B is incorrect). Tiratricol is an herbal product with thyroid hormone activity which can lower the required levothyroxine dose if used in combination (answer D is incorrect). See text in section "Hypothyroidism Drug-Drug and Drug-Food Interactions."

14. **B.** Food decreases the absorption of levothyroxine, and many foods, vitamins, and medications can lead to decreased levothyroxine absorption. Thus, it is recommended that levothyroxine be administered 30 minutes before breakfast (answer B is correct). For patients who cannot regularly take levothyroxine before breakfast, it is recommended to take it 30 minutes before or 2 hours after meals or administration of interacting products (answer C is incorrect). Many patients may need calcium or iron supplements for the treatment of other conditions; it is not reasonable to recommend discontinuing these agents in all clinical scenarios (answer A is incorrect). Certain medications for osteoporosis are recommended to be taken on an empty stomach before breakfast and require the patient to remain upright for 30 minutes to avoid esophageal irritation. While levothyroxine is recommended to be taken before breakfast on an empty stomach, it is not necessary to remain upright for a specified period of time (answer D is incorrect). See text in section "Hypothyroidism Drug-Drug and Drug-Food Interactions."

15. **D.** 50% to 85% of women treated with levothyroxine require an increase in their dose during pregnancy. This is due to multiple pregnancy-related factors, including the increased production of thyroid-binding proteins (answer D is correct). The volume of distribution is increased during pregnancy and is not a major factor in the need for levothyroxine dose adjustments (answer C is incorrect). T_4 and T_3 production is increased in

pregnant patients without preexisting hypothyroidism. However, for patients requiring levothyroxine treatment, hCG and TSH are unable to stimulate adequate T_4 production, so increases to exogenous levothyroxine doses are needed (answer B is incorrect). Placental deiodinase degradation is a contributing factor to the increased thyroid hormone requirements during pregnancy, but this leads to increased (not decreased) levothyroxine dosing needs (Answer A is incorrect). See text in sections "Special Populations" and "Hypothyroidism During Pregnancy."