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Hyperthyroidism and Thyrotoxicosis

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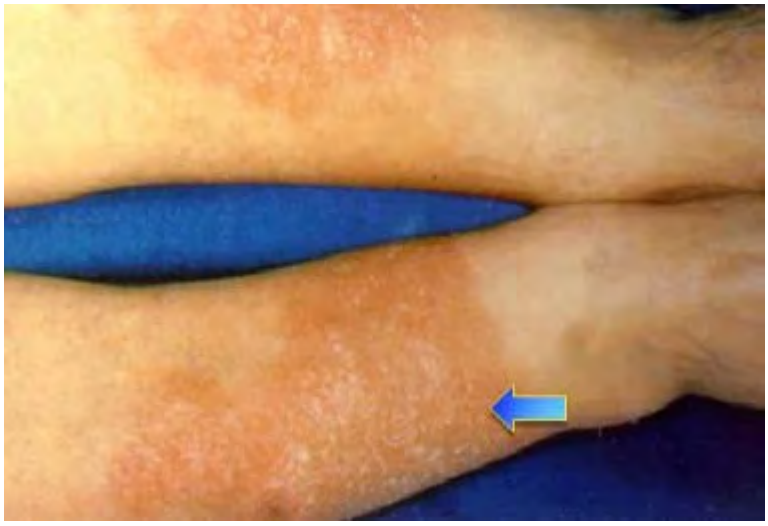
Overview

Practice Essentials

Hyperthyroidism is a set of disorders that involve excess synthesis and secretion of thyroid hormones by the thyroid gland, which leads to the hypermetabolic condition of thyrotoxicosis.[1, 2] The most common forms of hyperthyroidism include diffuse toxic goiter (Graves disease), toxic multinodular goiter (Plummer disease), and toxic adenoma. In thyrotoxicosis, thyroid hormone levels are elevated with or without increased thyroid hormone synthesis. The most common forms of thyrotoxicosis are caused by excess intake of the thyroid hormone medication levothyroxine or result from a temporary excess release of thyroid hormone due to subacute thyroiditis. The most reliable screening measure of thyroid function is the thyroid-stimulating hormone (TSH) level. Treatment of hyperthyroidism includes symptom relief, as well as antithyroid pharmacotherapy, radioactive iodine-131 (131I) therapy (the preferred treatment of hyperthyroidism among US thyroid specialists), or thyroidectomy. Thyrotoxicosis from subacute thyroiditis is temporary and self-resolving, and the treatment is also symptom relief. See the image below.



Bilateral erythematous infiltrative plaques on lower extremities in 42-year-old man with Graves disease are consistent with pretibial myxedema. Myxedematous changes of skin usually occur in pretibial areas and resemble orange peel in color and texture.

Signs and symptoms

Common symptoms of hyperthyroidism and thyrotoxicosis include the following:

- Nervousness
- Anxiety
- Increased perspiration

- Heat intolerance
- Hyperactivity
- Palpitations

Common signs of hyperthyroidism and thyrotoxicosis include the following:

- Tachycardia or atrial arrhythmia
- Systolic hypertension with wide pulse pressure
- Warm, moist, smooth skin
- Lid lag
- Stare
- Hand tremor
- Muscle weakness
- Weight loss despite increased appetite (although a few patients may gain weight, if excessive intake outstrips weight loss)
- Reduction in menstrual flow or oligomenorrhea

Presentation of thyrotoxicosis varies, as follows[3] :

- Younger patients tend to exhibit symptoms of sympathetic activation (eg, anxiety, hyperactivity, tremor)
- Older patients have more cardiovascular symptoms (eg, dyspnea, atrial fibrillation) and unexplained weight loss
- Patients with Graves disease often have more marked symptoms than patients with thyrotoxicosis from other causes
- Ophthalmopathy (eg, periorbital edema, diplopia, or proptosis) and pretibial myxedema dermopathy specifically occur with Graves disease
- Elevated thyroid hormone levels associated with subacute thyroiditis may occur as part of a postviral syndrome (subacute granulomatous thyroiditis) or within a year of the end of a pregnancy (postpartum subacute thyroiditis)

See Clinical Presentation for more detail.

Diagnosis

Thyroid function tests for hyperthyroidism and thyrotoxicosis are as follows:

- Thyroid-stimulating hormone (TSH)
- Free thyroxine (FT4) or free thyroxine index (FTI—total T4 multiplied by the correction for thyroid hormone binding)
- Total triiodothyronine (T3)

Thyroid function study results in hyperthyroidism and thyrotoxicosis are as follows:

- Hyperthyroidism and thyrotoxicosis are marked by suppressed TSH levels and elevated T3 and T4 levels
- Patients with milder hyperthyroidism may have elevation of T3 levels only with a suppressed TSH level
- Subclinical hyperthyroidism features decreased TSH and normal T3 and T4 levels

Autoantibody tests for hyperthyroidism are as follows:

- Anti–thyroid peroxidase (anti-TPO) antibody - Elevation with autoimmune thyroid disease found in 85% of Graves patients
- Thyroid-stimulating antibody (TSab) - Also known as thyroid-stimulating immunoglobulin (TSI), long-acting thyroid stimulator (LATS), or TSH-receptor antibody (TRab); found in 63-81% of Graves disease; a positive test is diagnostic and specific for Graves disease

Autoantibody titers in hyperthyroidism and thyrotoxicosis are as follows:

- Graves disease - Significantly elevated anti-TPO, elevated TSI ab
- Toxic multinodular goiter - Low or absent anti-TPO and negative TSI ab
- Toxic adenoma - Low or absent anti-TPO and negative TSI ab
- Patients without active thyroid disease may have mildly positive anti-TPO and TSI ab
- Subacute thyroiditis - Low or absent anti-TPO and negative TSI ab

If the etiology of elevated thyroid hormone levels is not clear after physical examination and other laboratory tests, it can be confirmed by scintigraphy: the degree and pattern of isotope uptake indicate the type of thyroid disorder. Findings are as follows:

- Graves disease – Diffuse enlargement of both thyroid lobes, with uniform uptake of isotope and elevated radioactive iodine uptake
- Toxic multinodular goiter -- Irregular areas of relatively diminished and occasionally increased uptake; overall radioactive iodine uptake is mildly to moderately increased
- Subacute thyroiditis – Very low radioactive iodine uptake, either with a painful thyroid (subacute granulomatous thyroiditis) or occurring within a year of pregnancy (postpartum subacute thyroiditis)

See Workup for more detail.

Management

Treatment of hyperthyroidism and thyrotoxicosis includes symptom relief, while hyperthyroidism also requires therapy with antithyroid medications, radioactive iodine-131 (131I), or thyroidectomy. Symptomatic treatment is as follows:

- Oral rehydration for dehydrated patients
- Beta-blockers for relief of neurologic and cardiovascular symptoms
- For mild ophthalmopathy, saline eye drops as needed and tight-fitting sunglasses for outdoors
- For vision-threatening ophthalmopathy, high-dose glucocorticoids, with consideration of orbital decompression surgery, ocular radiation therapy, or a recently approved treatment from the US Food and Drug Administration (FDA), teprotumumab-trbw, a monoclonal antibody that blocks the insulin-like growth factor-1 receptor (IGF-1R) and ameliorates proptosis by reducing inflammation and preventing muscle and fat-tissue remodeling in the orbit

Antithyroid drug treatment is as follows:

- Used for long-term control of hyperthyroidism in children, adolescents, and pregnant women
- In adult men and nonpregnant women, used to control hyperthyroidism before definitive therapy with radioactive iodine
- Methimazole is more potent and longer-acting than propylthiouracil
- Propylthiouracil is reserved for use in thyroid storm, first trimester of pregnancy, and methimazole allergy or intolerance
- Antithyroid drug doses are titrated every 4 weeks until thyroid functions normalize
- Patients with Graves disease may experience remission after treatment for 12-18 months, but recurrences are common within the following year
- Toxic multinodular goiter and toxic adenoma will not go into remission

Radioactive iodine treatment is as follows:

- Preferred therapy for hyperthyroidism
- Administered orally as a single dose in capsule or liquid form
- Causes fibrosis and destruction of the thyroid over weeks to many months
- Hypothyroidism is expected

- Pregnancy, breast feeding, and recent lactation are contraindications
- Radioactive iodine should be avoided in children younger than 5 years[4]
- Radioactive iodine is usually not given to patients with severe ophthalmopathy
- Radioactive iodine is usually not given to patients who cannot comply with physician restrictions for avoidance of radiation exposure to others

Thyroidectomy is reserved for special circumstances, including the following:

- Severe hyperthyroidism in children
- Pregnant women who are noncompliant with or intolerant of antithyroid medication
- Patients with very large goiters or severe ophthalmopathy
- Patients who refuse radioactive iodine therapy
- Refractory amiodarone-induced hyperthyroidism
- Patients who require normalization of thyroid functions quickly, such as pregnant women, women who desire pregnancy in the next 6 months, or patients with unstable cardiac conditions

Guidelines for the management of hyperthyroidism and other causes of thyrotoxicosis were developed by the American Thyroid Association and the American Association of Clinical Endocrinologists;[4] these were updated in 2016.[5]

See Treatment and Medication for more detail.

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Background

Hyperthyroidism is a set of disorders that involve excess synthesis and secretion of thyroid hormones by the thyroid gland. The resulting elevation in levels of free thyroxine (FT4), free triiodothyronine (FT3), or both leads to the hypermetabolic condition of thyrotoxicosis.

Thus, although many clinicians (endocrinologists excluded) use the terms hyperthyroidism and thyrotoxicosis interchangeably, the 2 words have distinct meanings. For example, both exogenous thyroid hormone intake and subacute thyroiditis can cause thyrotoxicosis, but neither constitutes hyperthyroidism, because the conditions are not associated with new hormone production.

The most common forms of hyperthyroidism include diffuse toxic goiter (Graves disease), toxic multinodular goiter (Plummer disease), and toxic adenoma (see Etiology). Together with subacute thyroiditis, these conditions constitute 85-90% of all causes of elevated thyroid hormone levels.

The most reliable screening measure of thyroid function in the healthy ambulatory adult population is the TSH level. The degree of thyrotoxicosis is determined by measurement of thyroid hormone levels. Autoantibody testing, and nuclear thyroid scintigraphy in some cases, can provide useful etiologic information. (See Workup.)

Treatment of hyperthyroidism includes symptom relief, as well as therapy with antithyroid medications, radioactive iodine, or thyroidectomy. However, antithyroid medications are not effective in thyrotoxicosis from subacute thyroiditis, because these cases result from release of preformed thyroid hormone. (See Treatment.)

For further information, see Pediatric Hyperthyroidism and Subacute Thyroiditis.

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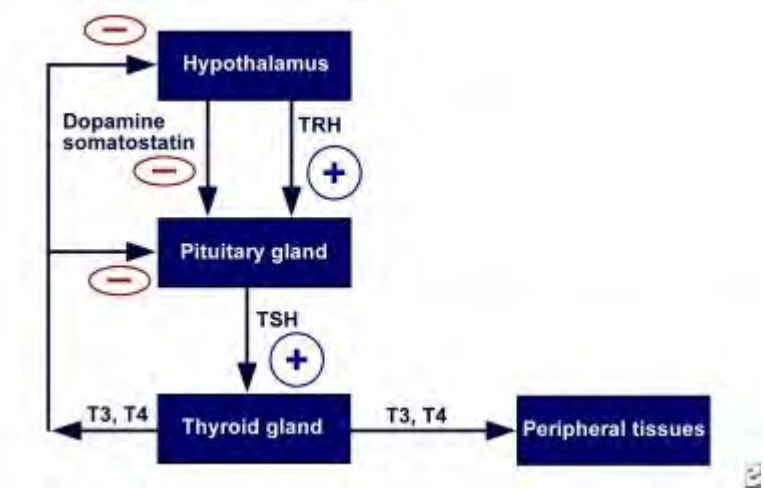
Pathophysiology

Normally, the secretion of thyroid hormone is controlled by a complex feedback mechanism involving the interaction of stimulatory and inhibitory factors (see the image below). Thyrotropin-releasing hormone (TRH) from the hypothalamus stimulates the pituitary to release TSH.



Hypothalamic-pituitary-thyroid axis feedback. Schematic representation of negative feedback system that regulates thyroid hormone levels. TRH = thyrotropin-releasing hormone; TSH = thyroid-stimulating hormone.

Binding of TSH to receptors on the thyroid gland leads to the release of thyroid hormones—primarily T4 and to a lesser extent T3. In turn, elevated levels of these hormones act on the hypothalamus to decrease TRH secretion and thus the synthesis of TSH.

Synthesis of thyroid hormone requires iodine. Dietary inorganic iodide is transported into the gland by an iodide transporter, converted to iodine, and bound to thyroglobulin by the enzyme thyroid peroxidase through a process called organification. This results in the formation of monoiodotyrosine (MIT) and diiodotyrosine (DIT), which are coupled to form T3 and T4; these are then stored with thyroglobulin in the thyroid's follicular lumen. The thyroid contains a large supply of its preformed hormones.

Thyroid hormones diffuse into the peripheral circulation. More than 99.9% of T4 and T3 in the peripheral circulation is bound to plasma proteins and is inactive. Free T3 is 20-100 times more biologically active than free T4. Free T3 acts by binding to nuclear receptors (DNA-binding proteins in cell nuclei), regulating the transcription of various cellular proteins.

Any process that causes an increase in the peripheral circulation of unbound thyroid hormone can cause thyrotoxicosis. Disturbances of the normal homeostatic mechanism can occur at the level of the pituitary gland, the thyroid gland, or in the periphery. Regardless of etiology, the result is an increase in transcription in cellular proteins, causing an increase in the basal metabolic rate. In many ways, signs and symptoms of hyperthyroidism resemble a state of catecholamine excess, and adrenergic blockade can improve these symptoms.

In Graves disease, a circulating autoantibody against the thyrotropin receptor provides continuous stimulation of the thyroid gland. This stimulatory immunoglobulin is diagnostic for Graves disease and has been called long-acting thyroid stimulator (LATS), thyroid-stimulating immunoglobulin (TSI), thyroid-stimulating antibody (TSab), and TSH-receptor antibody (TRab).[6] These antibodies stimulate the production and release of thyroid hormones and thyroglobulin; they also stimulate iodine uptake, protein synthesis, and thyroid gland growth. Anti–thyroid peroxidase (anti-TPO) antibody is assessed in a nonspecific test for autoimmune thyroid disease. Although the anti-TPO antibody is not diagnostic for Graves disease, it is present in 85% of patients with the disorder and can be quickly measured in local laboratories.[7]

Ophthalmopathy

The underlying pathophysiology of Graves ophthalmopathy (also called thyroid-associated orbitopathy) is not completely characterized. It most likely involves an antibody reaction against the TSH receptor that results in activation of T cells against tissues in the retro-orbital space that share antigenic epitopes with thyroid follicular cells.

These immune processes lead to an active phase of inflammation, with lymphocyte infiltration of the orbital tissue and release of cytokines that stimulate orbital fibroblasts to multiply and produce mucopolysaccharides (glycosaminoglycans), which absorb water. In consequence, the extraocular muscles thicken and the adipose and connective tissue of the retro-orbit increase in volume.

Cigarette smoking and a high TSH-receptor autoantibody level are significant risk factors for ophthalmopathy. In addition, patients who smoke appear to be more likely to experience worsening of their ophthalmopathy if treated with radioactive iodine, as do patients who have high pretreatment T3 levels and posttherapy hypothyroidism.

Etiology

Genetic factors appear to influence the incidence of thyrotoxicosis. Autoimmune thyroid disease, including Hashimoto hypothyroidism and Graves disease, often occurs in multiple members of a family.

Several genetic syndromes have been associated with hyperthyroidism, especially autoimmune thyroid disease. McCune-Albright syndrome is caused by mutations in the GNAS gene. This gene encodes the stimulatory G-protein alpha subunit, which is a key component of many signal transduction pathways. Patients present with the classic triad of polyostotic fibrous dysplasia, irregular café-au-lait spots, and precocious puberty. The syndrome may also include facial asymmetry, Cushing syndrome, hyperthyroidism, and acromegaly.[8]

A number of disorders of thyroid function have been found to be caused by mutations in the TSHR gene, which encodes the TSH receptor protein. These disorders include the following:

- Familial gestational hyperthyroidism
- One type of nonimmune hyperthyroidism
- Congenital nongoiterous thyrotoxicosis
- Toxic thyroid adenoma with somatic mutation

Type II autoimmune polyendocrine syndrome is associated with hyperthyroidism and hypothyroidism, as well as type 1 diabetes mellitus and adrenal insufficiency. Patients may also have immune deficiency, as manifested by chronic mucosal candidiasis.[9]

Autoimmune thyroid disease has a higher prevalence in patients with human leukocyte antigen (HLA)-DRw3 and HLA-B89. Graves disease is felt to be an HLA-related, organ-specific defect in suppressor T-cell function. Similarly, subacute painful or granulomatous thyroiditis occurs more frequently in patients with HLA-Bw35. Like other immune diseases, these thyroid conditions occur more frequently in women than in men.

With the availability of genome-wide association studies, more than a dozen genes and gene regions have been found to be associated with an increased risk for development of thyrotoxicosis, particularly Graves disease.[10, 11, 12, 13, 14, 15] Unsurprisingly, these studies have shown associations between these same genes and the development of other endocrine autoimmune disorders, such as type 1 diabetes mellitus.

The loci for which specific function can be deduced appear to involve genes related to HLA, non-HLA immune function, and thyroid function.[14] However, the odds ratios that have been determined generally indicate only a mildly increased risk for Graves disease.

Most of the genome-wide association studies have focused on diffuse toxic goiter (ie, Graves disease). One study, however, found an association between development of toxic multinodular goiter (Plummer disease) and a single-nucleotide polymorphism (SNP) in the TSHR gene.[16] . This SNP was seen in 9.6% of normal patients, 16.3% of patients with Graves disease, and 33.3% of patients with toxic multinodular goiter.

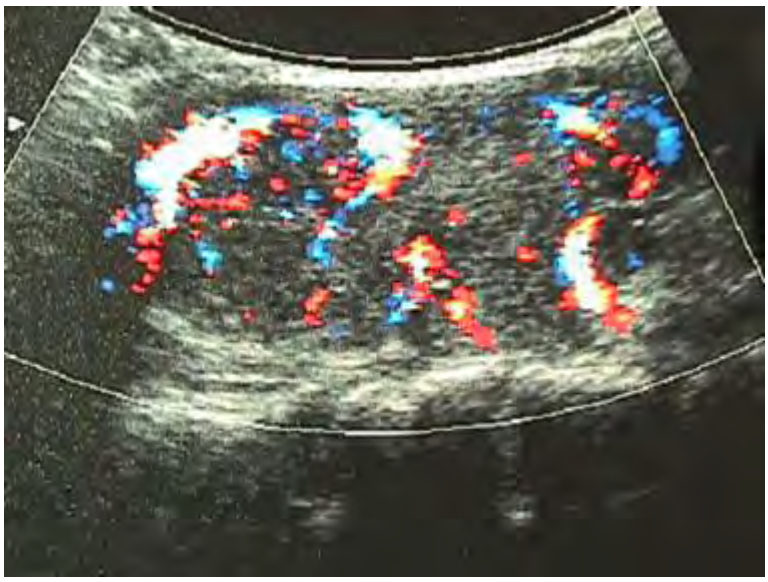
Iodine intake

Iodine intake also appears to influence the occurrence of thyrotoxicosis. Clearly, patients in borderline iodine-deficient areas of the world develop nodular goiter, often with areas of thyroid autonomy. When members of this population move to areas of sufficient iodine intake, thyrotoxicosis occurs. Evidence exists that iodine can act as an immune stimulator, precipitating autoimmune thyroid disease and acting as a substrate for additional thyroid hormone synthesis.

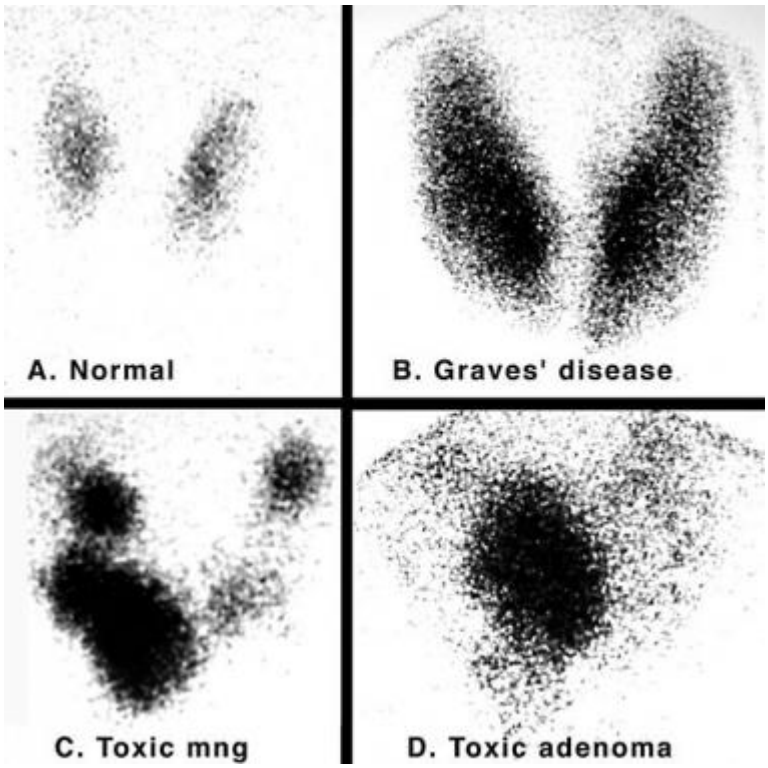
Graves disease

The most common cause of thyrotoxicosis is Graves disease (50-60% of cases). Graves disease is an organ-specific autoimmune disorder characterized by a variety of circulating antibodies, including common autoimmune antibodies, as well as anti-TPO and anti-TG antibodies.

The most important autoantibody is thyroid-stimulating antibody (TSab; also called TSI, LATS, or TRab), which is directed toward epitopes of the TSH receptor and acts as a TSH-receptor agonist. Like TSH, TSab binds to the TSH receptor on the thyroid follicular cells to activate thyroid hormone synthesis and release and thyroid gland growth (hypertrophy). This results in the characteristic picture of Graves thyrotoxicosis, with a diffusely enlarged thyroid, very high radioactive iodine uptake, and excessive thyroid hormone levels compared with a healthy thyroid (see the images below).



Color flow ultrasonogram in patient with Graves disease. Generalized hypervascularity is visible throughout gland (note red areas), which often can be heard as hum or bruit with stethoscope.



Iodine 123 (123I) nuclear scintigraphy: 123I scans of normal thyroid gland (A) and common hyperthyroid conditions with elevated radioiodine uptake, including Graves disease (B), toxic multinodular goiter (C), and toxic adenoma (D).

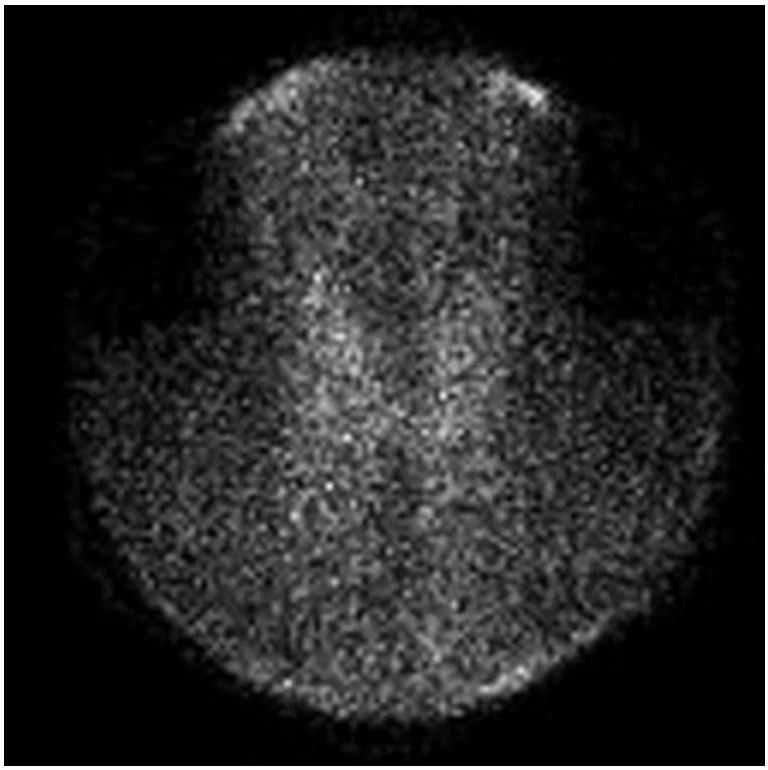
Thyroid hormone levels can be highly elevated in Graves disease. Clinical findings specific to Graves disease include thyroid ophthalmopathy (periorbital edema, chemosis [conjunctival edema], injection, or proptosis) and, rarely, dermopathy over the lower extremities. This autoimmune condition may be associated with other autoimmune diseases, such as pernicious anemia, myasthenia gravis, vitiligo, adrenal insufficiency, celiac disease, and type 1 diabetes mellitus.

In pregnant women with Graves disease, fetal or neonatal thyrotoxicosis can result from maternal TSH-receptor antibodies (TRabs) crossing the placenta. A literature review by van Dijk et al indicated that during pregnancy, neonatal thyrotoxicosis is a risk when the concentration of maternal TRabs reaches 4.4 U/L, a level 3.7 times the upper limit of normal.[17]

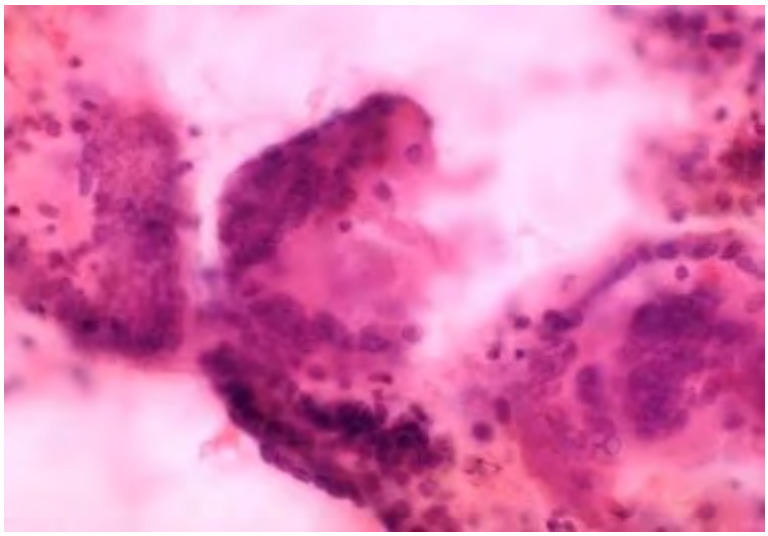
Subacute thyroiditis

The next most common cause of thyrotoxicosis is subacute thyroiditis (approximately 15-20% of cases), a destructive release of preformed thyroid hormone. A typical nuclear scintigraphy scan shows no radioactive iodine uptake (RAIU) in the thyrotoxic

phase of the disease (see the images below). Thyroid hormone levels can be highly elevated in this condition.



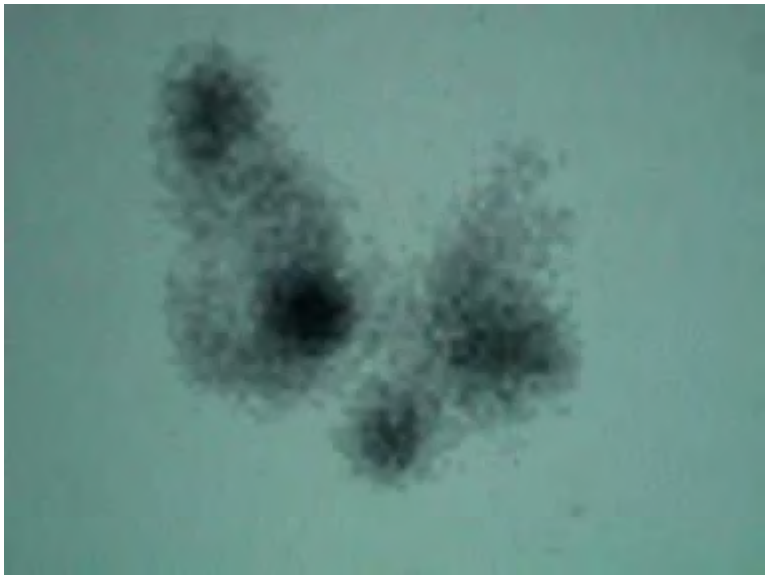
Absence of iodine 123 (123I) radioactive iodine uptake in patient with thyrotoxicosis and subacute painless or lymphocytic thyroiditis. Laboratory studies at time of scan demonstrated the following: thyroid-stimulating hormone (TSH), less than 0.06 mIU/mL; total thyroxine (T4), 21.2 µg/dL (reference range, 4.5-11); total triiodothyronine (T3), 213 ng/dL (reference range, 90-180); T3-to-T4 ratio, 10; and erythrocyte sedimentation rate (ESR), 10 mm/hr. Absence of thyroid uptake, low T3-to-T4 ratio, and low ESR confirm diagnosis of subacute painless thyroiditis.



Three multinuclear giant cell granulomas observed in fine-needle aspiration biopsy of thyroid from patient with thyrotoxicosis from subacute painful or granulomatous thyroiditis.

Toxic multinodular goiter

Toxic multinodular goiter (Plummer disease) accounts for 15-20% of thyrotoxicosis cases (see the image below). It occurs more commonly in elderly individuals, especially those with a long-standing goiter. Thyroid hormone excess develops very slowly over time and often is only mildly elevated at the time of diagnosis.



Scan in patient with toxic multinodular goiter. 5-Hour 123I-iodine uptake was elevated at 28% (normal 5-15%). Note multiple foci of variably increased tracer uptake.

Symptoms of thyrotoxicosis are mild, often because only a slight elevation of thyroid hormone levels is present, and the signs and symptoms of thyrotoxicosis often are blunted (apathetic hyperthyroidism) in older patients. However, very high thyroid hormone levels may occur in this condition after high iodine intake (eg, with iodinated radiocontrast or amiodarone exposure).

Toxic adenoma

Toxic adenoma is caused by a single hyperfunctioning follicular thyroid adenoma. This disorder accounts for approximately 3-5% of thyrotoxicosis cases. The excess secretion of thyroid hormone occurs from a benign monoclonal tumor that usually is larger than 2.5 cm in diameter. The excess thyroid hormone suppresses TSH levels. RAIU usually is normal, and the radioactive iodine scan shows only the hot nodule, with the remainder of the normal thyroid gland suppressed because the TSH level is low.

Other causes of thyrotoxicosis

Several rare causes of thyrotoxicosis exist that deserve mention. Struma ovarii is ectopic thyroid tissue associated with dermoid tumors or ovarian teratomas that can secrete excessive amounts of thyroid hormone and produce thyrotoxicosis.[18]

Iodide-induced thyrotoxicosis (Jod-Basedow syndrome) occurs in patients with excessive iodine intake (eg, from an iodinated radiocontrast study). The antiarrhythmic drug amiodarone, which is rich in iodine and bears some structural similarity to T4, may cause thyrotoxicosis (see Thyroid Dysfunction Induced by Amiodarone Therapy). Iodide-induced thyrotoxicosis also occurs in patients with areas of thyroid autonomy, such as a multinodular goiter or autonomous nodule.

Iodide-induced thyrotoxicosis appears to result from loss of the normal adaptation of the thyroid to iodide excess. It is treated with cessation of the excess iodine intake and with administration of antithyroid medication. Usually, after depletion of the excess iodine, thyroid functions return to preexposure levels.

Patients with a molar hydatidiform pregnancy or choriocarcinoma have extremely high levels of beta human chorionic gonadotropin (β-hCG), which can weakly activate the TSH receptor. At very high levels of β-hCG, activation of the TSH receptors is sufficient to cause thyrotoxicosis.

Metastatic follicular thyroid carcinoma may also result in thyrotoxicosis. These lesions maintain the ability to make thyroid hormone, and in patients with bulky tumors, production may be high enough to cause thyrotoxicosis.

Epidemiology

Graves disease is the most common form of hyperthyroidism in the United States, causing approximately 60-80% of cases of thyrotoxicosis. The annual incidence of Graves disease was found to be 0.5 cases per 1000 population during a 20-year period, with the peak occurrence in people aged 20-40 years.[19]

Toxic multinodular goiter (15-20% of thyrotoxicosis) occurs more frequently in regions of iodine deficiency. Most persons in the United States receive sufficient iodine, and the incidence of toxic multinodular goiter in the US population is lower than that in areas of the world with iodine deficiency. Toxic adenoma is the cause of 3-5% of cases of thyrotoxicosis.

The incidences of Graves disease and toxic multinodular goiter change with iodine intake. Compared with regions of the world with less iodine intake, the United States has more cases of Graves disease and fewer cases of toxic multinodular goiters.

Race-, sex-, and age-related demographics

Autoimmune thyroid disease occurs with the same frequency in Caucasians, Hispanics, and Asians but at lower rates in African Americans.

All thyroid diseases occur more frequently in women than in men. Graves autoimmune disease has a male-to-female ratio of 1:5-10. The male-to-female ratio for toxic multinodular goiter and toxic adenoma is 1:2-4. Graves ophthalmopathy is more common in women than in men.

Autoimmune thyroid diseases have a peak incidence in people aged 20-40 years. Toxic multinodular goiters occur in patients who usually have a long history of nontoxic goiter and who therefore typically present when they are older than age 50 years. Patients with toxic adenomas present at a younger age than do patients with toxic multinodular goiter.

Mortality and morbidity

A literature review by Varadharajan and Choudhury indicated that the rate of thyroid cancer associated with hyperthyroidism is not insignificant. In patients who underwent surgery for Graves disease, toxic adenoma, or toxic multinodular goiter, the mean overall rate of thyroid cancer was found to be 8.5%. The mean rates, specifically, for malignancy in Graves disease, toxic adenoma, and toxic multinodular goiter were 5.9%, 6.5%, and 12%, respectively. Regarding cancer subtype, the mean rates for papillary thyroid cancer, micropapillary carcinoma, and follicular thyroid cancer were 3.1%, 5.1%, and 0.8%, respectively.[20]

A study by Kim et al reported hyperthyroidism to be a risk factor for myocardial infarction and ischemic stroke in females, persons aged 50 years or older, and nonobese individuals, independent of cardiovascular risk factors. However, hyperthyroidism was not found to significantly impact mortality secondary to cardiovascular events.[21]

Prognosis

Hyperthyroidism from toxic multinodular goiter and toxic adenoma is permanent and usually occurs in adults. After normalization of thyroid function with antithyroid medications, radioactive iodine ablation usually is recommended as the definitive therapy. Long-term, high-dose antithyroid medication is not recommended. Toxic multinodular goiters and toxic adenomas probably will continue to grow slowly in size during antithyroid pharmacotherapy.

Generally, the thyrotoxic areas are ablated, and patients may remain euthyroid. Those who become hypothyroid after radioactive iodine therapy are easily maintained on thyroid hormone replacement therapy, with T4 taken once daily.

Patients with Graves disease may become hypothyroid in the natural course of their disease, regardless of whether treatment involves radioactive iodine or surgery. Eye disease may develop at a time distant from the initial diagnosis and therapy. Generally, after the diagnosis, the ophthalmopathy slowly improves over years.

Thyroid hormone excess causes left ventricular thickening, which is associated with an increased risk of heart failure and cardiac-related death. Thyrotoxicosis has been associated with dilated cardiomyopathy,[22] right heart failure with pulmonary hypertension, and diastolic dysfunction and atrial fibrillation.[23]

An increase in the rate of bone resorption occurs. Bone loss, measured by bone mineral densitometry, can be seen in severe hyperthyroidism at all ages and in both sexes. In mild subclinical disease, however, bone loss has been convincingly shown only in postmenopausal women.

A study by Zhyzhneuskaya et al of patients with subclinical hyperthyroidism due to Graves disease suggested that approximately one third will progress to overt hyperthyroidism, about one third will develop normalized thyroid function, and just under one third will remain in a state of subclinical hyperthyroidism. (One person in the study became hypothyroid.) Multivariate regression analysis indicated that risk of progression to overt hypothyroidism is greater in patients with older age or a positive anti–thyroid peroxidase antibody status. The study included 44 patients, with follow-up lasting at least 12 months.[24]

Presentation

History

The presentation of thyrotoxicosis is variable among patients. Thyrotoxicosis leads to an apparent increase in sympathetic nervous system symptoms. Younger patients tend to exhibit symptoms of sympathetic activation, such as anxiety, hyperactivity, and tremor, while older patients have more cardiovascular symptoms, including dyspnea and atrial fibrillation with unexplained weight loss.[3] The clinical manifestations of thyrotoxicosis do not always correlate with the extent of the biochemical abnormality.

Common symptoms of hyperthyroidism and thyrotoxicosis include the following:

- Nervousness
- Anxiety
- Increased perspiration
- Heat intolerance
- Hyperactivity
- Palpitations

Generally, a constellation of information, including the extent and duration of symptoms, past medical history, and social and family history, in addition to the information derived from physical examination, help to guide the clinician to the appropriate diagnosis. For example, Graves disease is an autoimmune disease, and patients often have a family history or past medical history of autoimmune disease (eg, rheumatoid arthritis, vitiligo, pernicious anemia).

Patients with Graves disease often have more marked symptoms than patients with thyrotoxicosis from other causes, because thyroid hormone levels usually are the highest with this form of hyperthyroidism. The diagnosis of Graves disease should also be considered if any evidence of thyroid eye disease exists, including periorbital edema, diplopia, or proptosis.

Toxic multinodular goiters occur in patients who have had a known nontoxic goiter for many years or decades. Often, patients have emigrated from regions of the world with borderline- low iodine intake or have a strong family history of nontoxic goiter.

Subclinical hyperthyroidism, defined as a low thyroid-stimulating hormone (TSH) level with normal free thyroxine (FT4) and free triiodothyronine (FT3) levels, is associated with no or minimal clinical symptoms of thyrotoxicosis. However, certain conditions (eg, atrial fibrillation, osteoporosis, or hypercalcemia) may suggest the possibility of thyrotoxicosis. In fact, subclinical hyperthyroidism may be associated with a 3-fold increase in the risk of atrial fibrillation. The prevalence of subclinical hyperthyroidism may be as high as 2% in the general population.

The risk of atrial fibrillation may be elevated even in persons with high-normal thyroid function. In a report from the Netherlands on 1426 patients whose TSH levels were in the normal range (0.4-4.0 mIU/L), the hazard ratio for atrial fibrillation was 1.94 for the lowest versus the highest quartile of TSH, after a median follow-up of 8 years.[25]

Radiation exposure increases the risk of benign and malignant nodular thyroid diseases, especially with the higher radiation levels used in radiation therapy. External radiation therapy is associated with an increase in the incidence of autoimmune hyperthyroidism when the thyroid is in the radiation field.

The family history should include careful documentation of the following:

- Autoimmune disease
- Thyroid disease
- Emigration from iodine-deficient parts of the world

Review a complete list of medications and dietary supplements. A number of compounds—including expectorants, amiodarone, iodinated contrast dyes, and health food supplements containing seaweed or thyroid gland extracts—contain large amounts of iodine that can induce thyrotoxicosis in a patient with thyroid autonomy. Rarely, iodine exposure can cause thyrotoxicosis in a patient with an apparently healthy thyroid.

Physical Examination

The thyroid is located in the lower anterior neck. The isthmus of the butterfly-shaped gland generally is located just below the cricoid cartilage of the trachea, with the wings of the gland wrapping around the trachea. Physical examination often can help the clinician to determine the etiology of thyrotoxicosis.

Common signs of hyperthyroidism and thyrotoxicosis include the following:

- Tachycardia or atrial arrhythmia
- Systolic hypertension with wide pulse pressure
- Warm, moist, smooth skin
- Lid lag
- Stare
- Hand tremor
- Muscle weakness
- Weight loss despite increased appetite (although a few patients may gain weight, if excessive intake outstrips weight loss)
- Reduction in menstrual flow or oligomenorrhea

Thyroid examination

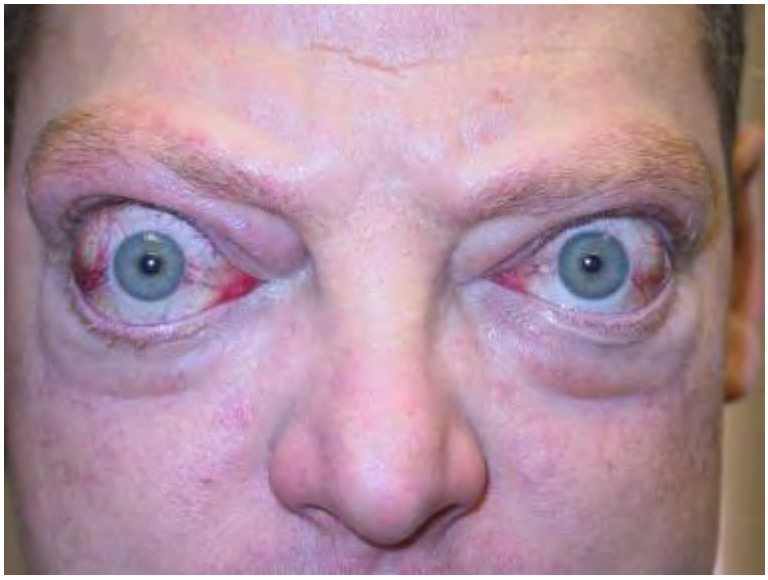
Thyrotoxicosis from Graves disease is associated with a diffusely enlarged and slightly firm thyroid gland. Sometimes, a thyroid bruit can be heard by using the bell of the stethoscope.

Toxic multinodular goiters generally occur when the thyroid gland is enlarged to at least 2 to 3 times the normal size. The gland often is soft, but individual nodules occasionally can be palpated. Because most thyroid nodules cannot be palpated, thyroid nodules should be documented by thyroid ultrasonography, but overactive thyroid nodules can be demonstrated only by nuclear thyroid imaging with radioiodine (I-123) or technetium (Tc99m) thyroid scan.

If the thyroid is enlarged and painful, subacute painful or granulomatous thyroiditis is the likely diagnosis. However, degeneration or hemorrhage into a nodule and suppurative thyroiditis should also be considered.

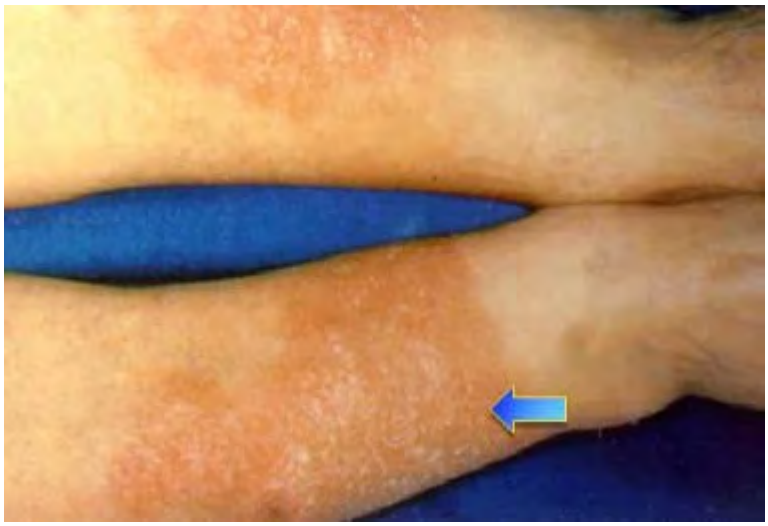
Ophthalmologic and dermatologic examination

Approximately 50% of patients with Graves thyrotoxicosis have mild thyroid ophthalmopathy. Often, this is manifested only by periorbital edema, but it also can include conjunctival edema (chemosis), injection, poor lid closure, extraocular muscle dysfunction (diplopia), and Proptosis (see the image below). Evidence of thyroid eye disease and high thyroid hormone levels confirms the diagnosis of autoimmune Grave disease.



Severe proptosis, periorbital edema, and eyelid retraction from thyroid-related orbitopathy. This patient also had optic nerve dysfunction and chemosis (conjunctival edema) from thyroid-related orbitopathy.

In rare instances, Graves disease affects the skin through deposition of glycosaminoglycans in the dermis of the lower leg. This causes nonpitting edema, which is usually associated with erythema and thickening of the skin, without pain or pruritus (see the image below).



Bilateral erythematous infiltrative plaques on lower extremities in 42-year-old man with Graves disease are consistent with pretibial myxedema. Myxedematous changes of skin usually occur in pretibial areas and resemble orange peel in color and texture.

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Diagnostic Considerations

Diagnostic considerations include factitious hyperthyroidism, which is hyperthyroidism secondary to intentional consumption of thyroid hormone. In this condition, thyroid hormone consumption causes suppression of thyroglobulin secretion by the thyroid. Factitious hyperthyroidism is common in medical personnel, who have easy access to medication containing thyroid hormone and may abuse it for weight loss or an energy boost.

Differential Diagnoses

- Diffuse Toxic Goiter (Graves Disease)
- Euthyroid Hyperthyroxinemia
- Goiter
- Graves Disease
- Struma Ovarii
- Thyrotoxicosis Imaging

Workup

Approach Considerations

The most reliable screening measure of thyroid function is the thyroid-stimulating hormone (TSH) level. TSH levels usually are suppressed to unmeasurable levels (< 0.05 µIU/mL) in thyrotoxicosis. The degree of thyrotoxicosis is determined by measurement of thyroid hormone levels; the severity of clinical manifestations often does not correlate with the degree of thyroid hormone elevation.

The most specific autoantibody test for autoimmune thyroiditis is an enzyme-linked immunosorbent assay (ELISA) test for anti–thyroid peroxidase (anti-TPO) antibody. The titers usually are significantly elevated in the most common type of hyperthyroidism, Graves thyrotoxicosis, and usually are low or absent in toxic multinodular goiter and toxic adenoma.

If the etiology of elevated thyroid hormone levels is not clear after physical examination and other laboratory tests, it can be confirmed by means of scintigraphy. The degree and pattern of isotope uptake indicate the type of thyroid disorder.

Older patients with hyperthyroidism often present with atrial arrhythmias or heart failure. Electrocardiography is recommended if an irregular or elevated (> 100 beats/min) heart rate or signs of heart failure are noted upon examination.

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TSH and Thyroid Hormone Levels

Although measurement of the TSH level is the most reliable screening method for assessing thyroid function, the degree of thyrotoxicosis cannot be estimated easily in this way. Instead, thyrotoxicosis must be measured using an assay of thyroid hormone levels in the plasma.

Thyroid hormone circulates as triiodothyronine (T3) and thyroxine (T4), with more than 99.9% of the hormones bound to serum proteins (especially thyroxine-binding globulin, transthyretin or thyroxine-binding prealbumin, and albumin). Measuring free T4 (FT4) and total T3 is recommended in patients with suspected thyrotoxicosis when TSH is low. Patients with milder hyperthyroidism may have elevation of T3 levels only, with suppressed TSH.

Many laboratories do not measure FT4 directly, instead using a calculation to estimate the FT4 level. The free thyroxine index (FTI) is equal to total T4 multiplied by the correction for thyroid hormone binding, such as the thyroid hormone–binding ratio (THBR) or T3 resin uptake [T3 RU]). A similar calculation can be used with total T3.

Hyperthyroidism and thyrotoxicosis are marked by TSH levels suppressed below the reference range (usually 0.4-4 mIU/L) and elevated thyroid hormone levels. Subclinical hyperthyroidism is defined as a decreased but not undetectable TSH level (< 0.5 µIU/mL in many laboratories) in combination with serum concentrations of T3 and T4 that are within the reference range. Because nonthyroidal illness will produce temporary suppression of TSH, thyroid function tests should be repeated before therapy is instituted for subclinical disease.

Hormonal changes in pregnancy can complicate the interpretation of thyroid function tests. Physiologic maximum elevation of beta human chorionic gonadotropin (β-hCG) at the end of the first trimester of pregnancy is associated with a mirror-image temporary reduction in TSH. Despite the reduction in TSH, FT4 levels usually remain normal or only slightly above the reference range. As the pregnancy progresses and β-hCG plateaus at a lower level, TSH levels return to normal.

Elevated thyroid hormone levels associated with subacute thyroiditis may occur as part of a postviral syndrome (subacute granulomatous thyroiditis) or within a year of the end of a pregnancy (postpartum subacute thyroiditis).

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Autoantibody Studies

The most specific autoantibody test for autoimmune thyroiditis is an ELISA test for anti-TPO antibody. The titers usually are significantly elevated in the most common type of hyperthyroidism, Graves thyrotoxicosis, and usually are low or absent in toxic multinodular goiter and toxic adenoma. A significant number of healthy people without active thyroid disease have mildly positive anti-TPO antibody titers; thus, the test should not be performed for screening purposes.

The thyroid-stimulating immunoglobulin (TSI) level, if elevated, helps to establish the diagnosis of Graves disease. Circulating antithyroglobulin (anti-TG) antibodies are also present in Graves disease; however, testing for these antibodies should not be used, because anti-TG antibodies by themselves may be present in persons without other evidence of thyroid dysfunction.[26]

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Scintigraphy

If the etiology of elevated thyroid hormone levels is not clear after physical examination and other laboratory tests, it can be confirmed by means of scintigraphy. Iodine-123 (123I) or technetium-99m (99mTc) can be used for thyroid scanning. Normally, the isotope distributes homogeneously throughout both lobes of the thyroid gland. In patients with hyperthyroidism, the pattern of uptake (eg, diffuse vs nodular) varies with the underlying disorder.

The overall level of radioactive iodine uptake (RAIU) also varies with different conditions. Normal RAIU is approximately 5-20% but is modified by the iodine content of the patient's diet (see Table 1 below).

Table 1. Thyrotoxicosis and Hyperthyroidism (Open Table in a new window)

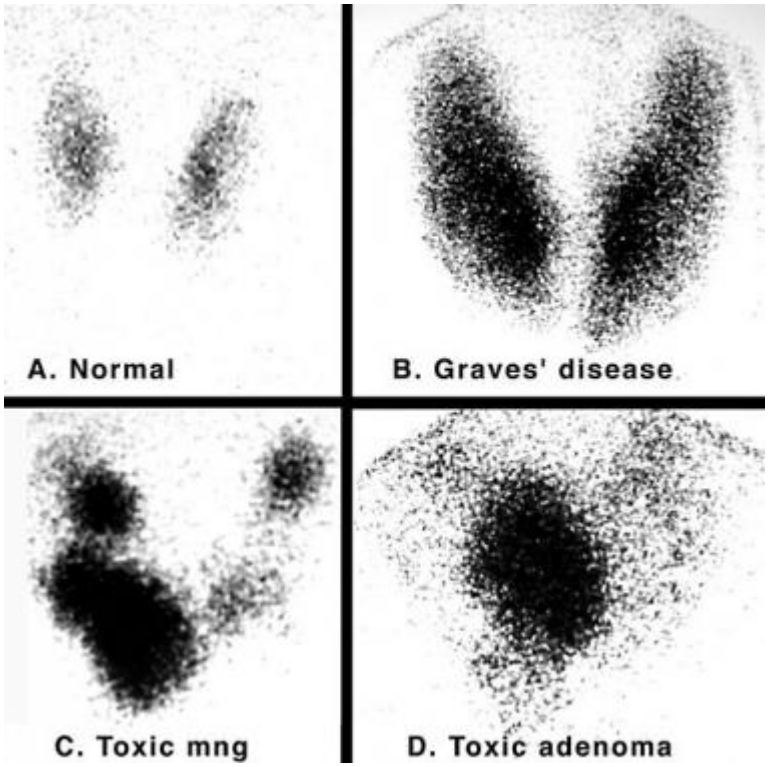
Common Forms (85-90% of Cases)	24-Hour RAIU Over Neck*
Diffuse toxic goiter (Graves disease)	Increased (moderate to high: 40-100%)
Toxic multinodular goiter (Plummer disease)	Increased (mild to moderate: 25-60%)
Thyrotoxic phase of subacute thyroiditis	Decreased (very low: < 2%)
Toxic adenoma	Increased (mild to moderate: 25-60%)
Less Common Forms	
Iodide-induced thyrotoxicosis	Variable but usually low (< 25%)

Thyrotoxicosis factitia	Decreased (very low: < 2%)
Uncommon Forms	
Pituitary tumors producing TSH	Increased (mild to moderate: 25-60%)
Excess human chorionic gonadotropin (molar pregnancy/choriocarcinoma)	Increased (variable: 25-100%)
Pituitary resistance to thyroid hormone	Increased (mild to moderate: 25-60%)
Metastatic thyroid carcinoma	Decreased
Struma ovarii with thyrotoxicosis	Decreased

RAIU = radioactive iodine uptake; TSH = thyroid-stimulating hormone.

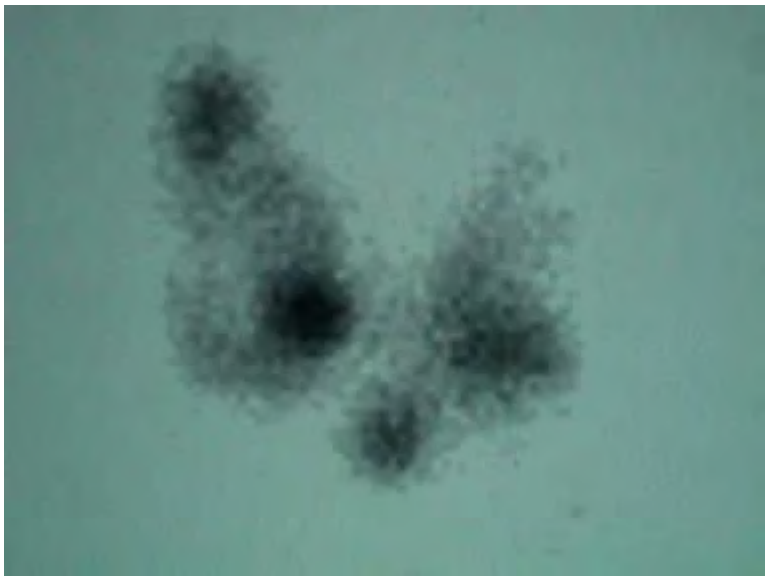
* A normal 6-hour RAIU is approximately 2-16%; a 24-hour RAIU is about 8-25% but is modified according to the iodine content of the patient’s diet. RAIU or scanning should not be performed in a woman who is pregnant (with the exception of a molar pregnancy) or breastfeeding.

In Graves disease, scintigraphy shows diffuse enlargement of both thyroid lobes, with uniform uptake of isotope (see the image below). Overall RAIU is elevated.



Iodine 123 (123I) nuclear scintigraphy: 123I scans of normal thyroid gland (A) and common hyperthyroid conditions with elevated radioiodine uptake, including Graves disease (B), toxic multinodular goiter (C), and toxic adenoma (D).

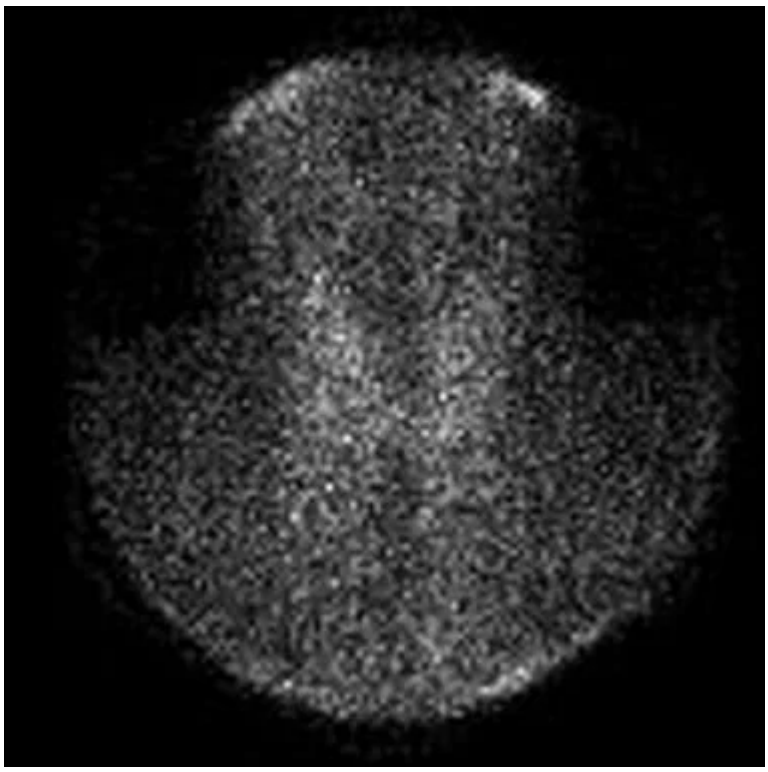
Toxic multinodular goiters are characterized by irregular areas of relatively diminished and occasionally increased uptake (see the image below). Overall RAIU is mildly to moderately increased.



Scan in patient with toxic multinodular goiter. 5-Hour 123I-iodine uptake was elevated at 28% (normal 5-15%). Note multiple foci of variably increased tracer uptake.

The classification of nodules as "hot," "warm," or "cold" is determined by their isotope-concentrating ability relative to the surrounding normal parenchyma. Autonomously functioning thyroid nodules are "hot" compared with normal thyroid tissue. If a dominant nodule is found upon examination of a patient with thyrotoxicosis, and scintigraphy shows that the nodule is cold, an ultrasound-guided fine-needle aspiration (FNA) biopsy of the nodule should be performed to exclude concomitant malignancy.

In subacute thyroiditis (see the image below), radioactive iodine uptake is very low (approximately 1-2%). Occasionally, Hashimoto hypothyroidism can be associated with normal, elevated, or suppressed radioactive iodine uptake.



Absence of iodine 123 (123I) radioactive iodine uptake in patient with thyrotoxicosis and subacute painless or lymphocytic thyroiditis. Laboratory studies at time of scan demonstrated the following: thyroid-stimulating hormone (TSH), less than 0.06 mIU/mL; total thyroxine (T4), 21.2 µg/dL (reference range, 4.5-11); total triiodothyronine (T3), 213 ng/dL (reference range, 90-180); T3-to-T4 ratio, 10; and erythrocyte sedimentation rate (ESR), 10 mm/hr. Absence of thyroid uptake, low T3-to-T4 ratio, and low ESR confirm diagnosis of subacute painless thyroiditis.

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Treatment

Approach Considerations

Treatment of hyperthyroidism and thyrotoxicosis includes symptom relief, while hyperthyroidism also requires antithyroid pharmacotherapy, radioactive iodine-131 (131I) therapy (the preferred treatment of hyperthyroidism among US thyroid specialists), or thyroidectomy. However, antithyroid medications are not effective in thyrotoxicosis in which scintigraphy shows low uptake of iodine-123 (123I), as in patients with subacute thyroiditis, because these cases result from release of preformed thyroid hormone.

If a physician treats enough patients who are hyperthyroid, eventually he or she will encounter a patient who develops agranulocytosis or hepatitis from the antithyroid medications. Discussing these adverse effects with patients before starting therapy is important; accordingly, patients should be given written or documented verbal instruction to the effect that if they develop high fever (>100.5°F) or a severe sore throat, they should stop the medication and seek medical attention.

Guidelines for the management of hyperthyroidism and other causes of thyrotoxicosis were developed by the American Thyroid Association (ATA) and the American Association of Clinical Endocrinologists;[4] these were updated in 2016.[5]

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Management of Ophthalmopathy

Although 50% of patients with Graves disease have mild signs and symptoms of thyroid eye disease, only 5% develop severe ophthalmopathy (eg, diplopia, visual-field deficits, or blurred vision).[4] Less serious ophthalmologic symptoms (eg, photophobia,

irritation, and tearing) are treated with tight-fitting sunglasses, which should be worn at all times when the patient is outside, and with saline eye drops that are taken as necessary for comfort.

If exposure keratitis is suspected, the patient should be monitored by an ophthalmologist. This condition usually occurs when eyelid closure is incomplete and the cornea is exposed at night, when the patient does not blink. Typically, patients complain of irritation and tearing on awakening. Treatment includes administering saline gel or drops and taping eyelids closed with paper tape before sleep. Some ophthalmologists are concerned about corneal abrasion from the tape and instead recommend that patients wear goggles at night to keep the eyes moist.

A medical emergency occurs when sufficient orbital edema exists to cause optic nerve compression with early loss of color vision and orbital pain. Without treatment, continued pressure on the optical nerve may cause permanent vision loss. High-dose glucocorticoids are administered, with consideration given to orbital decompression surgery, ocular radiation therapy, or a recently approved treatment from the US Food and Drug Administration (FDA), teprotumumab-trbw, a monoclonal antibody that blocks the insulin-like growth factor-1 receptor (IGF-1R) and ameliorates proptosis by reducing inflammation and preventing muscle and fat-tissue remodeling in the orbit.

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Management of Dermopathy

Infiltrative dermopathy, usually developing over the lower extremities, is characterized by an accumulation of glycosaminoglycans and inflammatory cells in the dermis. The skin changes typically include a nonpitting erythematous edema of the anterior shins. Dermopathy can occur at other sites of repeat trauma. The dermopathy usually occurs only in the presence of significant ophthalmopathy.

No effective treatment exists. Nightly occlusive wraps of the affected site are recommended, with plastic wrap used after the application of a high-potency topical steroid cream.

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Relief of Symptoms

Many of the neurologic and cardiovascular symptoms of thyrotoxicosis are relieved by beta-blocker therapy. Before such therapy is initiated, the patient should be examined for signs and symptoms of dehydration that often occur with hyperthyroidism. After oral rehydration, beta-blocker therapy can be started. Beta-blocker therapy should not be administered to patients with a significant history of asthma.

Calcium channel blockers (eg, verapamil and diltiazem) can be used for the same purposes when beta-blockers are contraindicated or poorly tolerated. These therapies should be tapered and stopped once thyroid functions are within the normal range.

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Antithyroid Pharmacotherapy

Antithyroid drugs (eg, methimazole and propylthiouracil) have been used for hyperthyroidism since their introduction in the 1940s. These medications are employed for long-term control of hyperthyroidism in children, adolescents, and pregnant women. In adult men and nonpregnant women, they are used to control hyperthyroidism before definitive therapy with radioactive iodine.

Antithyroid medications inhibit the formation and coupling of iodotyrosines in thyroglobulin. Because these processes are necessary for thyroid hormone synthesis, this inhibition induces a gradual reduction in thyroid hormone levels over 2-8 weeks or longer. A second action of propylthiouracil (but not methimazole) is inhibition of conversion of thyroxine (T4) to triiodothyronine (T3). T3 is more biologically active than T4; thus, a quick reduction in T3 levels is associated with a clinically significant improvement in thyrotoxic symptoms.

The antithyroid drug dose should be titrated every 4 weeks until thyroid functions normalize. Some patients with Graves disease go into a remission after treatment for 12-18 months, and the drug can be discontinued. Notably, half of the patients who go into remission experience a recurrence of hyperthyroidism within the following year. Nodular forms of hyperthyroidism (ie, toxic multinodular goiter[27] and toxic adenoma) are permanent conditions and will not go into remission.

Methimazole is more potent than propylthiouracil and has a longer duration of action. In addition, methimazole is taken once daily, whereas propylthiouracil is taken 2-3 times daily; consequently, patient compliance is often better with methimazole than with propylthiouracil.

Methimazole is not recommended for use in the first trimester of pregnancy, because it has been associated (albeit rarely) with cloacal and scalp (cutis aplasia) abnormalities when given during early gestation.[4, 28] Generally, if a nonpregnant woman who is receiving methimazole desires pregnancy, she should be switched to propylthiouracil before conception. After 12 weeks of gestation, she can be switched back to methimazole, with frequent monitoring.

Propylthiouracil remains the drug of choice in uncommon situations of life-threatening severe thyrotoxicosis (ie, thyroid storm) because of the additional benefit of inhibition of T4-to-T3 conversion. In this setting, propylthiouracil should be administered every 6-8 hours. The reduction in T3, which is 20-100 times more potent than T4, theoretically helps reduce the thyrotoxic symptoms more quickly than methimazole would. Once thyroid levels have decreased to nearly normal values, the patient can be switched to methimazole therapy.

Except in thyroid storm, propylthiouracil is considered a second-line drug therapy. It is reserved for use in patients who are allergic to or intolerant of methimazole and in women who are in the first trimester of pregnancy or planning pregnancy.

Adverse effects of antithyroid medications

The most common adverse effects of antithyroid drugs are allergic reactions manifesting as fever, rash, urticaria, and arthralgia, which occur in 1-5% of patients, usually within the first few weeks of treatment. Serious adverse effects include agranulocytosis, aplastic anemia, hepatitis, polyarthritis, and a lupuslike vasculitis. All of these adverse effects, except agranulocytosis, occur more frequently with propylthiouracil: agranulocytosis occurs in 0.2-0.5% of patients overall and is no more common with one drug than with the other.

Patients with agranulocytosis usually present with fever and pharyngitis. After the drug is stopped, granulocyte counts usually start to rise within several days but may not normalize for 10-14 days. Granulocyte colony-stimulating factor (G-CSF) appears to accelerate recovery in patients with a bone marrow aspiration showing a granulocyte-to-erythrocyte ratio of 1:2 or greater than 0.5.

In 2010, the US Food and Drug Administration (FDA) added a boxed warning, the strongest warning issued by the FDA, to the prescribing information for propylthiouracil. The warning emphasized the risk for severe liver injury and acute liver failure, some cases of which have been fatal.[29] Severe liver injury has rarely been reported with methimazole (5 cases, 3 of which resulted in death).

The FDA recommends the following measures for patients receiving propylthiouracil (for more information, see the FDA Safety Alert)[29] :

- Closely monitor patients for signs and symptoms of liver injury, especially during the first 6 months after initiation of therapy
- For suspected liver injury, promptly discontinue propylthiouracil, evaluate the patient for evidence of liver injury, and provide supportive care
- Counsel patients to contact their health care provider promptly for the following signs or symptoms: fatigue, weakness, vague abdominal pain, loss of appetite, itching, easy bruising, or yellowing of the eyes or skin

Other drugs

In severe thyrotoxicosis from Graves disease or subacute thyroiditis, iodine or iodinated contrast agents have been administered to block the conversion of T4 to T3 and the release of thyroid hormone from the gland. This therapy is reserved for severe thyrotoxicosis because its use prevents definitive therapy for Graves thyrotoxicosis with radioactive iodine for many weeks.

A saturated solution of potassium iodide (SSKI) can be administered at a dosage of 10 drops twice daily, with a consequent rapid reduction in T3 levels. Iopanoic acid/ipodate at a dosage of 1 g/day is also effective; it has not been available in the United States for several years but is available in some areas of Europe.

These drugs must not be administered to patients with toxic multinodular goiter or toxic adenomas. The autonomous nature of these conditions can lead to worsening of the thyrotoxicosis in the presence of pharmacologic levels of iodide, a substrate in thyroid hormone synthesis. This phenomenon typically presents in patients living in iodine deficient areas who relocate to an iodine sufficient geographical area or upon ingestion of iodine (Jod-Basedow syndrome).

Another drug that might be considered in management of severe thyrotoxicosis would be cholestyramine, a bile salt sequestrant. It decreases thyroid hormone levels by depleting the pool by enhancing clearance from enterohepatic circulation.

Doses up to 12 grams in 3 divided daily dose have been used for 4 weeks.

Radioactive Iodine Therapy

Radioactive iodine therapy[30] is the most common treatment for Graves disease in adults in the United States. Although its effect is less rapid than that of antithyroid medication or thyroidectomy, it is effective and safe and does not require hospitalization.

A literature review by Wang and Qin of randomized, controlled trials indicated that compared with antithyroid drugs, radioiodine treatment has a higher cure rate for Graves disease and is associated with a lower recurrence rate. However, it was also found to carry a greater risk for the development or worsening of ophthalmopathy and for hypothyroidism.[31]

Concerns about radiation exposure after therapy have led to the issuance of new recommendations by the ATA. These recommendations are compliant with Nuclear Regulatory Commission regulations and are a practical guide for patient activity after radioactive iodine therapy, with the aim of ensuring maximum radiation safety for the family and the public.[32]

Radioactive iodine is administered orally as a single dose in capsule or liquid form. The iodine is quickly absorbed and taken up by the thyroid. No other tissue or organ in the body is capable of retaining the radioactive iodine; consequently, very few adverse effects are associated with this therapy. The treatment results in a thyroid-specific inflammatory response, causing fibrosis and destruction of the thyroid over weeks to many months.

Generally, the dose of 131I administered is 75-200 µCi/g of estimated thyroid tissue divided by the percent of 123I uptake in 24 hours. This dose is intended to render the patient hypothyroid.

Administration of lithium in the weeks following radioactive iodine therapy may extend the retention of radioactive iodine and increase its efficacy. This may be considered in Graves disease patients with especially large Graves glands (>60 g) or in patients with extremely high thyroidal iodine uptake (>95% in 4 hours), which is associated with high iodine turnover in the gland. However, studies have yielded inconsistent results, and the benefits of using lithium with radioactive iodine must be weighed against the toxicities associated with lithium.

Hypothyroidism is considered by many experts to be the expected goal of radioactive iodine therapy. In several large epidemiologic studies of radioactive iodine therapy in patients with Graves disease, no evidence indicated that radioactive iodine therapy caused the development of thyroid carcinoma. There is also no evidence that radioactive iodine therapy for hyperthyroidism results in increased mortality for any other form of cancer, including leukemia.

Long-term follow-up data of children and adolescents treated with radioactive iodine are lacking. ATA guidelines recommend avoiding 131I therapy in children younger than 5 years of age. In children 5 to 10 years old, 131I therapy is acceptable if the calculated activity of administered 131I is less than 10 mCi. In children older than 10 years of age, radioactive iodine therapy is acceptable if the activity is greater than 150 µCi/g of thyroid tissue.

Radioactive iodine should never be administered to pregnant women, because it can cross the placenta and ablate the fetus's thyroid, resulting in hypothyroidism. Similarly, breastfeeding is a contraindication, in that the radioisotope is secreted in breast milk. Women will continue to receive increased radiation to the breast from radioactive iodine for a few months after ceasing lactation; accordingly, initiation of this therapy should be delayed.

It is standard practice to check for pregnancy before starting radioactive iodine therapy and to recommend that the patient not become pregnant for at least 3-6 months after the treatment or until thyroid functions normalize. No excess fetal malformations or increased miscarriage rates have been found in women previously treated with radioactive iodine for hyperthyroidism.

Radioactive iodine usually is not administered to patients with severe ophthalmopathy, because clinical evidence suggests that worsening of thyroid eye disease occurs after radioactive iodine therapy. This worsening is usually mild but occasionally severe. Moreover, radioactive iodine usually is not given to patients who cannot comply with physician restrictions for avoidance of radiation exposure to others.

The risk of ophthalmopathy is greater in patients who smoke cigarettes, but it can be reduced by providing glucocorticoid therapy (prednisone 0.4 mg/kg for 1 month with subsequent taper) after radioactive iodine therapy.

Thyroidectomy

Subtotal thyroidectomy is the oldest form of treatment for hyperthyroidism. Total thyroidectomy and combinations of hemithyroidectomies and contralateral subtotal thyroidectomies also have been used.[30, 33]

Because of the excellent efficacy of antithyroid medications and radioactive iodine therapy in regulating thyroid function, thyroidectomy is generally reserved for special circumstances, including the following:

- Severe hyperthyroidism in children
- Pregnant women who are noncompliant with or intolerant of antithyroid pharmacotherapy
- Patients with very large goiters or severe ophthalmopathy
- Patients who refuse radioactive iodine therapy
- Patients with refractory amiodarone-induced hyperthyroidism
- Patients who require normalization of thyroid functions quickly, such as pregnant women, women who desire pregnancy in the next 6 months, or patients with unstable cardiac conditions

Preparation for thyroidectomy includes antithyroid medication, stable (cold) iodine treatment, and beta-blocker therapy.[33] Generally, antithyroid drug therapy should be administered until thyroid functions normalize (4-8 weeks). Propranolol is titrated until the resting pulse rate is lower than 80 beats/min. Finally, iodide is administered as SSKI (1-2 drops twice daily for 10-14 days) before the procedure. Stable iodide therapy both reduces thyroid hormone excretion and decreases thyroid blood flow, which may help reduce intraoperative blood loss.

A Swiss study found that administration of a single dose of steroid (dexamethasone 8 mg) before thyroidectomy can reduce the nausea, pain, and vomiting associated with the procedure, as well as improve voice function.[34] Benefits were most pronounced in the first 16 hours after the operation. Postoperative steroid administration is not considered to be the standard of care for thyroid surgery in the United States.

With current operative techniques, bilateral subtotal thyroidectomy should have a mortality approaching zero in patients who are properly prepared. Historically, operative stress was the most common cause of thyroid storm, a physiologic decompensation in patients who are severely thyrotoxic, with a mortality of about 50%. Adverse effects of thyroidectomy include recurrent laryngeal nerve damage and hypoparathyroidism from damage to local structures during the procedure.

A literature review by Zhang et al comparing endoscopic with conventional open thyroidectomy for Graves disease reported that the endoscopic technique offers better cosmetic satisfaction and less blood loss, while open surgery is associated with reduced operation time. Complication rates for the two techniques with regard to transient recurrent laryngeal nerve palsy, recurrent hyperthyroidism, hypothyroidism, and transient hypocalcemia were equivalent.[35]

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Diet and Activity

No special diet must be followed by patients with thyroid disease. However, some expectorants, radiographic contrast dyes, seaweed tablets, and health food supplements contain excess amounts of iodide and should be avoided because the iodide interferes with or complicates the management of antithyroid and radioactive iodine therapies.

Exercise tolerance often is not significantly affected in otherwise healthy patients with mild to moderate hyperthyroidism. For these patients, no reduction in physical activity is necessary. For patients who are elderly or have cardiopulmonary comorbidities or severe hyperthyroidism, a decrease in activity is prudent until hyperthyroidism is medically controlled.

With severe thyrotoxicosis, systolic and diastolic cardiac dysfunction often result in dyspnea on exertion. Beta-blocker therapy often greatly improves exercise tolerance until thyroid hormones levels are reduced by other therapies.

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Consultations

Generally, thyrotoxicosis should be evaluated and treated by an endocrinologist. Therapy, including radioactive iodine and antithyroid medication, requires careful follow-up, which is best performed by a specialist.

Generally, after definitive therapy is completed with radioactive iodine or surgical thyroidectomy, the patient can be cared for by a primary care physician. These patients may require thyroid hormone replacement therapy.

Patients with Graves thyrotoxicosis should be examined by an ophthalmologist for moderate or symptomatic thyroid eye disease, which occurs in some form in 50% of patients. Often, the eye disease is subclinical and remits with time. The eye disease usually occurs within 1 year before or after the diagnosis of hyperthyroidism, but new-onset disease has been detected decades later. Graves eye disease also can occur without the patient ever having developed hyperthyroidism.

Long-Term Monitoring

Care after initiation of antithyroid medication

After 4-6 weeks, antithyroid medications usually must be reduced; otherwise, the patient becomes hypothyroid. Hypothyroidism causes the usual symptoms of fatigue and weight gain, and in patients with Graves disease, it has been anecdotally associated with worsening of thyroid ophthalmopathy. Initially, the patient should have thyroid function tests performed every 4-6 weeks until thyroid hormone levels are stabilized on a low dosage of antithyroid medication.

Patients with non-Graves hyperthyroidism rarely experience remissions. In patients who are placed on long-term antithyroid drug therapy with the goal of remission, follow-up tests of thyroid function should be performed at least every 3 months for the first year.

In patients with Graves disease, antithyroid medication should be stopped or decreased after 12-18 months to determine whether the patient has gone into remission. In these patients, remission is defined as a normal TSH level after cessation of antithyroid drug therapy.

Once a patient with Graves hyperthyroidism becomes euthyroid on oral antithyroid medication, other definitive treatment, such as radioactive iodine therapy or surgery, should be considered. Although a significant fraction of patients with Graves disease go into remission, as many as 20% become hypothyroid over subsequent years as a consequence of autoimmune destruction of the gland.

Care after radioactive iodine ablation

Ablation of the gland occurs over 2-5 months after radioactive iodine therapy. Most patients become hypothyroid. Checking thyroid functions every 4-6 weeks until the patient stabilizes is recommended.

Once the thyroid hormone levels start falling into the low-normal range, it is reasonable to stop antithyroid medications and to consider starting low-dose thyroid hormone replacement before the patient becomes hypothyroid; however, some physicians prefer to document persistently elevated TSH values with the patient off antithyroid medication before starting thyroid hormone replacement.

Starting with partial or low-dose thyroid hormone replacement is recommended (50-75 µg/day, adjusted every 6-8 weeks to normalize the TSH level). Several weeks after 131I therapy, patients can, in rare cases, become thyrotoxic as a result of vigorous thyroid destruction and release of preformed hormone. This process often is accompanied by a painful, radiation-induced thyroiditis that can be treated with nonsteroidal anti-inflammatory drugs (NSAIDs) or glucocorticoids.

In addition, radioablation can cause the release of thyroid antigens and exacerbate the autoimmune thyroid disease process. In such cases, Graves disease can worsen.

Care after thyroid surgery

Patients whose thyroid functions normalize after surgery require routine follow-up because hypothyroidism (from the chronic thyroiditis), recurrent hyperthyroidism, or thyroid eye disease may develop at some time in the future. Most patients remain euthyroid after a lobectomy or lobectomy plus isthmusectomy to treat a toxic adenoma or toxic multinodular goiter with a dominant nodule. To ensure normal thyroid function, thyroid function tests should be obtained 3-4 weeks after a lobectomy.

After subtotal thyroidectomy for hyperthyroidism and cessation of antithyroid therapy, most patients become hypothyroid, depending on how much functional tissue is left by the surgeon. Partial replacement (T4 50-75 µg/day) is recommended in these patients, beginning shortly after the procedure. Thyroid function tests should be monitored 4-8 weeks postoperatively, and the T4 dosage should be adjusted to maintain a normal TSH level.

Guidelines

Guidelines Summary

In 2016, the American Thyroid Association (ATA) updated the 2011 hyperthyroidism/thyrotoxicosis guidelines it had codeveloped with the American Association of Clinical Endocrinologists. The following are a sampling of the 124 evidence-based recommendations included in the guideline update[5] :

- Beta-adrenergic blockade is recommended in all patients with symptomatic thyrotoxicosis, especially elderly patients and thyrotoxic patients with resting heart rates in excess of 90 beats per minute or coexistent cardiovascular disease
- Patients with overt Graves hyperthyroidism should be treated with any of the following modalities: radioactive iodine therapy, antithyroid drugs, or thyroidectomy
- If methimazole is chosen as the primary therapy for Graves disease, the medication should be continued for approximately 12-18 months and then discontinued if the serum thyrotropin and thyrotropin receptor antibody levels are normal at that time
- If surgery is chosen as the primary therapy for Graves disease, near-total or total thyroidectomy is the procedure of choice
- If surgery is chosen as treatment for toxic multinodular goiter, near-total or total thyroidectomy should be performed
- If surgery is chosen as the treatment for toxic adenoma, a thyroid sonogram should be done to evaluate the entire thyroid gland; an ipsilateral thyroid lobectomy (or isthmusectomy, if the adenoma is in the thyroid isthmus), should be performed for isolated toxic adenomas
- Children with Graves disease should be treated with methimazole, radioactive iodine therapy, or thyroidectomy; radioactive iodine therapy should be avoided in very young children (< 5 years); radioactive iodine therapy in children is acceptable if the activity is over 150 µCi/g (5.55 MBq/g) of thyroid tissue and for children between ages 5 and 10 years if the calculated radioactive iodine administered activity is under 10 mCi (< 473 MBq); thyroidectomy should be chosen when definitive therapy is required, the child is too young for radioactive iodine, and surgery can be performed by a high-volume thyroid surgeon
- If methimazole is chosen as the first-line treatment for Graves disease in children, it may be tapered in those children requiring low doses after 1-2 years to determine if a spontaneous remission has occurred, or it may be continued until the child and caretakers are ready to consider definitive therapy, if needed
- If surgery is chosen as therapy for Graves disease in children, total or near-total thyroidectomy should be performed
- Euthyroidism should be expeditiously achieved and maintained in hyperthyroid patients with Graves orbitopathy or risk factors for the development of orbitopathy
- In patients with Graves hyperthyroidism who have mild active ophthalmopathy and no risk factors for deterioration of their eye disease, radioactive iodine therapy, antithyroid drugs, and thyroidectomy should be considered equally acceptable therapeutic options
- In Graves disease patients with mild Graves orbitopathy who are treated with radioactive iodine, steroid coverage is recommended if there are concomitant risk factors for Graves orbitopathy deterioration

In 2017, the American Thyroid Association released guidelines pertaining to the diagnosis and management of thyroid disease in women during pregnancy and the postpartum period, as well as prior to conception. Recommendations regarding thyrotoxicosis in pregnancy included the following[36] :

- When a suppressed serum TSH is detected in the first trimester (TSH less than the reference range), a medical history, physical examination, and measurement of maternal serum free thyroxine (FT4) or total thyroxine (T4) concentrations should be performed; measurement of thyroid-stimulating antibody (TSab) and maternal total triiodothyronine (T3) may prove helpful in clarifying the etiology of thyrotoxicosis
- Radionuclide scintigraphy or radioiodine uptake determination should not be performed in pregnancy
- The appropriate management of abnormal maternal thyroid tests attributable to gestational transient thyrotoxicosis and/or hyperemesis gravidarum includes supportive therapy, management of dehydration, and hospitalization if needed; antithyroid drugs are not recommended, though beta blockers may be considered
- In all women of childbearing age who are thyrotoxic, the possibility of future pregnancy should be discussed; women with Graves disease seeking future pregnancy should be counseled regarding the complexity of disease management during future gestation, including the association of birth defects with antithyroid drug use; preconception counseling should review the risks and benefits of all treatment options and the patient's desired timeline to conception
- Thyrotoxic women should be rendered stably euthyroid before attempting pregnancy; several treatment options exist, each of which is associated with risks and benefits; these include ^{131}I ablation, surgical thyroidectomy, and antithyroid drug therapy
- Women taking methimazole or propylthiouracil should be instructed to confirm potential pregnancy as soon as possible; if the pregnancy test is positive, pregnant women should contact their caregiver immediately
- In pregnant women with a high risk of developing thyrotoxicosis if antithyroid drugs were to be discontinued, continued antithyroid medication may be necessary; factors predicting high clinical risk include being currently hyperthyroid or

requirement of >5-10 mg/d methimazole or >100-200 mg/d propylthiouracil to maintain a euthyroid state; in such cases, propylthiouracil is recommended for the treatment of maternal hyperthyroidism through 16 weeks of pregnancy, and when shifting from methimazole to propylthiouracil, a dose ratio of approximately 1:20 should be used (e.g., methimazole 5 mg/d = propylthiouracil 50 mg twice daily)

- In women being treated with antithyroid drugs in pregnancy, free thyroxine (FT4)/total thyroxine (T4) and TSH should be monitored approximately every 4 weeks; antithyroid medication during pregnancy should be administered at the lowest effective dose of methimazole or propylthiouracil, targeting maternal serum free thyroxine (FT4)/total thyroxine (T4) at the upper limit of or moderately above the reference range.
- A combination regimen of levothyroxine (LT4) and an antithyroid drug should not be used in pregnancy, except in the rare situation of isolated fetal hyperthyroidism
- Thyroidectomy in pregnancy may be indicated for unique scenarios; if required, the optimal time for thyroidectomy is in the second trimester of pregnancy; if maternal thyroid-stimulating antibody (TSab) concentration is high (>3 times the upper reference for the assay), the fetus should be carefully monitored for development of fetal hyperthyroidism throughout pregnancy, even if the mother is euthyroid postthyroidectomy
- The ATA concurs with the American College of Obstetricians and Gynecologists' Committee on Obstetric Practice consensus guidelines (written in 2011 and revised in 2015), which state the following: ''1) A pregnant woman should never be denied indicated surgery, regardless of trimester. 2) Elective surgery should be postponed until after delivery. 3) If possible, nonurgent surgery should be performed in the second trimester when preterm contractions and spontaneous abortion are least likely.'' In the setting of a patient with Graves disease undergoing urgent, nonthyroid surgery, if the patient is well controlled on antithyroid medication, no other preparation is needed; beta blockade should also be utilized if needed
- If the patient has a past history of Graves disease treated with ablation (radioiodine or surgery), a maternal serum determination of thyroid-stimulating antibodies (TSabs) is recommended at initial thyroid function testing during early pregnancy
- If maternal thyroid-stimulating antibody (TSab) concentration is elevated in early pregnancy, repeat testing should occur at weeks 18-22
- If the patient requires treatment with antithyroid drugs for Graves disease through midpregnancy, a repeat determination of thyroid-stimulating antibody (TSab) concentration is again recommended at weeks 18-22
- If elevated thyroid-stimulating antibody (TSab) is detected at weeks 18-22 or the mother is taking antithyroid medication in the third trimester, a TSab measurement should again be performed in late pregnancy (weeks 30-34) to evaluate the need for neonatal and postnatal monitoring
- Fetal surveillance should be performed in women who have uncontrolled hyperthyroidism in the second half of pregnancy and in women with high thyroid-stimulating antibody (TSab) levels detected at any time during pregnancy (>3 times the upper limit of normal); a consultation with an experienced obstetrician or maternal–fetal medicine specialist is recommended; monitoring may include ultrasonography to assess heart rate, growth, amniotic fluid volume, and the presence of fetal goiter
- If antithyroid drug therapy is given for hyperthyroidism caused by autonomous nodules, the fetus should be carefully monitored for goiter and signs of hypothyroidism during the second half of pregnancy; a low dose of antithyroid medication should be administered with the goal of maternal free thyroxine (FT4) or total thyroxine (T4) concentration at the upper limit of or moderately above the reference range

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Medication

Medication Summary

Drug therapy includes medications that reduce the symptoms of thyrotoxicosis and decrease the synthesis and release of thyroid hormone. In the United States, the most common definitive therapy for hyperthyroidism is ablation of the hyperactive thyroid with an oral dose of radioactive iodine (131I).

In some cases the patient is treated with antithyroid medication to return thyroid hormone levels to normal. When that is accomplished, some patients (eg, those with a toxic multinodular goiter or toxic adenoma) are treated immediately with radioactive iodine, while patients with autoimmune Graves disease may be treated for 12-18 months with antithyroid medications because of the possibility that the patient will go into remission.

Patients with other forms of hyperthyroidism, including toxic multinodular goiter and toxic adenoma, continue to be thyrotoxic indefinitely. Remissions with antithyroid medications are not expected.

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Antithyroid Agents

Class Summary

Antithyroid agents inhibit the synthesis of thyroxine (T4) and triiodothyronine (T3).

Methimazole (Northyx, Tapazole)

With few exceptions, methimazole should be used in every patient who needs antithyroid drug therapy for hyperthyroidism. The exceptions are women in the first trimester of pregnancy, patients in thyroid storm, and patients with methimazole allergy or intolerance. Methimazole is avoided in early pregnancy because of increased placental transfer and risk of a rare fetal condition (cutis aplasia). Compared with propylthiouracil, it has a higher transfer rate into the milk of lactating women.

Methimazole inhibits thyroid hormone by blocking oxidation of iodine in the thyroid gland. However, it is not known to inhibit peripheral conversion of thyroid hormone. The drug is available as 5-mg or 10-mg tablets. It is readily absorbed and has a serum half-life of 6-8 hours. Methimazole is less protein-bound than propylthiouracil is.

Methimazole's duration of action is longer than its half-life, and the drug should be dosed every 12-24 hours. Studies have shown that rectal suppositories or retention enemas can be used at the same dose as orally administered methimazole for patients who cannot take oral medications. Usually, after thyroid function improves, the dose must be decreased or the patient will become hypothyroid.

Propylthiouracil (PropylThyracil, PTU)

Propylthiouracil is a derivative of thiourea that inhibits organification of iodine by the thyroid gland. It blocks oxidation of iodine in the thyroid gland, thereby inhibiting thyroid hormone synthesis; the drug inhibits T4-to-T3 conversion (and thus has an advantage over other agents).

Propylthiouracil remains the drug of choice in uncommon situations of life-threatening severe thyrotoxicosis. It may be preferable during and before the first trimester of pregnancy.

In 2010, the US Food and Drug Administration (FDA) added a boxed warning to the prescribing information for propylthiouracil, emphasizing the risk for severe liver injury and acute liver failure, some cases of which have been fatal.

Propylthiouracil is available as a 50-mg tablet. It is readily absorbed and has a serum half-life of 1-2 hours. It is highly protein-bound in the serum. The drug's duration of action is longer than its half-life, and propylthiouracil generally should be dosed every 6-8 hours (though it can also be administered twice daily). If patient compliance is an issue, methimazole may be a better choice because it can be given as a single daily dose in many cases.

Thyroid hormone levels (thyroid-stimulating hormone [TSH], T4, free thyroxine index [FTI] or free T4, and T3) should be reassessed in 4-6 weeks after starting propylthiouracil. The dosage is increased if thyroid hormone levels have not significantly fallen or decreased if thyroid hormone levels have fallen by 50% or more (even if the patient is still thyrotoxic).

Usually, after thyroid function improves, the dosage should be gradually decreased to 50-150 mg/day in divided doses. Otherwise, the patient will become hypothyroid.

Potassium iodide (SSKI, ThyroSafe, ThyroShield, iOSAT)

Potassium iodide inhibits thyroid hormone secretion. Iodide therapy is primarily used for the treatment of thyroid storm or given preoperatively, 10-14 days before surgical procedures (including thyroidectomy).

Until high levels of iodine build up in the thyroid follicular cell, however, administration of iodine can increase thyroid hormone synthesis and lead to higher serum levels of thyroid hormone. Thus, it is usually recommended that iodine not be started until after antithyroid drug therapy has been initiated. In thyroid storm, iodine should be administered at least 1 hour after methimazole or propylthiouracil.

Potassium iodide and iodine (Lugol's solution)

Lugol's solution is primarily administered for 10 days before thyroidectomy or during thyrotoxic crisis because high levels of iodine in the follicular thyroid cell temporarily inhibit thyroid hormone synthesis and secretion. T4 and T3 concentrations can be reduced for several weeks.

Until high levels of iodine build up in the thyroid follicular cell, however, administration of iodine can increase thyroid hormone synthesis and lead to higher serum levels of thyroid hormone. Thus, it is usually recommended that iodine not be started until after antithyroid drug therapy has been initiated.

Sodium iodide 131I (Iodotope, Hicon)

Radioactive iodine is approved by the FDA for treatment of hyperthyroidism in adults. It can also be used with a radioactive uptake test to evaluate thyroid function. The agent is quickly absorbed and taken up by the thyroid. No other tissue or organ in the body is capable of retaining radioactive iodine; therefore, few adverse effects develop.

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Beta Blockers, Nonselective

Class Summary

Nonselective beta blockers reduce many of the symptoms of thyrotoxicosis, including tachycardia, tremor, and anxiety. Usually, propranolol is recommended because of central nervous system (CNS) penetration, but some patients prefer longer-acting beta blockers. Patients note an immediate improvement in tachycardia, anxiety, heat intolerance, and tremor. Calcium channel blockers for tachycardia are sometimes used when beta blockers are contraindicated or not tolerated.

Propranolol (Inderal, Inderal LA, InnoPran XL)

Propranolol is the drug of choice for treating cardiac arrhythmias resulting from hyperthyroidism. It controls cardiac and psychomotor manifestations within minutes.

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Beta Blockers, Beta1-Selective

Class Summary

Beta blockers diminish hyperthyroid symptoms, such as tachycardia, tremor, and anxiety. Beta1 -selective drugs may be tolerated better in patients who have relative beta-blockade contraindications.

Atenolol (Tenormin)

Atenolol selectively blocks beta1 receptors, with little or no effect on beta2 types. It is a longer-acting drug that can be more useful than propranolol for intraoperative and postoperative control.

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Questions & Answers

Overview

What is hyperthyroidism?

What are the symptoms of hyperthyroidism and thyrotoxicosis?

What are the signs of thyrotoxicosis in hyperthyroidism?

What is the presentation of thyrotoxicosis in hyperthyroidism?

Which thyroid function tests are performed in the workup of hyperthyroidism and thyrotoxicosis?

DDX

Which conditions should be included in the differential diagnoses for hyperthyroidism?

What are the differential diagnoses for Hyperthyroidism and Thyrotoxicosis?

Workup

What is the most reliable screening measure of thyroid function?

What is the role of anti ? thyroid peroxidase (anti-TPO) antibody testing in the workup of hyperthyroidism?

What is the role of scintigraphy in the workup of hyperthyroidism?

What is the role of electrocardiography (EKG) in the workup of hyperthyroidism?

How is thyrotoxicosis measured in the workup of hyperthyroidism?

What is the role of thyroxine (T4) and triiodothyronine (T3) measurement in the workup of hyperthyroidism?

How is subclinical hyperthyroidism defined?

Which factors may complicate the interpretation of thyroid function tests in the workup of hyperthyroidism?

Is anti-thyroid peroxidase (anti-TPO) antibody testing used in hyperthyroidism screening?

What is the role of thyroid-stimulating immunoglobulin (TSI) measurement in the workup of hyperthyroidism?

What is role of scintigraphy in the workup of hyperthyroidism?

Which scintigraphy findings suggest Graves disease?

Which scintigraphy findings suggest toxic multinodular goiters?

How are nodules classified in scintigraphy results of hyperthyroidism?

Which scintigraphy findings suggest subacute thyroiditis?

Treatment

What are the treatment options for hyperthyroidism and thyrotoxicosis?

What are possible adverse effects of antithyroid medications for hyperthyroidism?

Which organizations have developed guidelines for the management of hyperthyroidism?

How are the ophthalmologic manifestations of hyperthyroidism treated?

What is the treatment for exposure keratitis in patients with hyperthyroidism?

What ophthalmologic emergency may occur in patients with hyperthyroidism?

What is the presentation of dermopathy (dermatologic symptoms) in patients with hyperthyroidism?

How is dermopathy treated in patients with hyperthyroidism?

What is the role of beta-blocker therapy in the treatment of hyperthyroidism?

What is the role of calcium channel blockers in the treatment of hyperthyroidism?

Which drugs are used in the treatment of hyperthyroidism?

How do antithyroid medications work to treat hyperthyroidism?

What is the dosage regimen for antithyroid medication in the treatment of hyperthyroidism?

What is the role of methimazole in the treatment of hyperthyroidism?

What is the role of propylthiouracil in the treatment of hyperthyroidism?

What monitoring is needed after thyroid surgery for hyperthyroidism?

Guidelines

What are the 2016 ATA guidelines for the management of hyperthyroidism/thyrotoxicosis?

What are the 2017 ATA guidelines for the diagnosis and management of thyroid disease in women during pregnancy, the postpartum period, and preconception?

Medications

What is the drug therapy for hyperthyroidism?

How are patients with hyperthyroidism treated?

Which patients with hyperthyroidism continue to be thyrotoxic after treatment with antithyroid medications?

Which medications in the drug class Beta Blockers, Beta1-Selective are used in the treatment of Hyperthyroidism and Thyrotoxicosis?

Which medications in the drug class Beta Blockers, Nonselective are used in the treatment of Hyperthyroidism and Thyrotoxicosis?

Which medications in the drug class Antithyroid Agents are used in the treatment of Hyperthyroidism and Thyrotoxicosis?

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