Hyperthyroidism

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Abstract

Hyperthyroidism has multiple etiologies, manifestations, and potential therapies and untreated cases may result in significant morbidity and mortality. Appropriate treatment requires an accurate diagnosis and is influenced by age, coexisting medical conditions and patient preference. The proper treatment of hyperthyroidism depends on recognition of the signs and symptoms of the disease and determination of the etiology. The most common cause of hyperthyroidism is Graves' disease. Other common causes include toxic multinodular goiter, toxic adenomas, thyroiditis and certain medications. The diagnostic workup should begin with a thyroid-stimulating hormone level test, the most sensitive screening test. There are many therapeutic modalities of hyperthyroidism and selection of these modalities depend upon the age, cause, prevailing medical condition and patient's preference. This chapter will provide an overview of hyperthyroidism in non-pregnant adults.

Introduction

Hyperthyroidism is characterized by inappropriately increased thyroid hormone synthesis and secretion. This overactive disease has many causes, myriad of clinical manifestations, and variety of therapies. The most common forms of hyperthyroidism include diffuse toxic goiter (Graves disease), toxic multinodular goiter (Plummer disease), and toxic adenoma. Together with subacute thyroiditis, these conditions account for 85–90 % of all causes of hyperthyroidism [1, 2].

The term "thyrotoxicosis" refers to a clinical state resulting from inappropriately high thyroid hormone action in tissues generally due to inappropriately high tissue thyroid hormone levels. The term "hyperthyroidism" is a form of thyrotoxicosis due to inappropriately high synthesis and secretion of thyroid hormone(s) by the thyroid. Although, many clinicians use the terms hyperthyroidism and thyrotoxicosis interchangeably, the 2 words have distinct meanings. For

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S.K. Imam, S.I. Ahmad (eds.), *Thyroid Disorders: Basic Science and Clinical Practice*,
DOI 10.1007/978-3-319-25871-3_8

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. It should also be noted that the elevation of free thyroid hormone levels does not always result in thyrotoxicosis.

As we know that iodine plays an important role in thyroid homeostasis (see Chap. 3 for detail description) and 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. 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.

Appropriate treatment of thyrotoxicosis requires an accurate diagnosis. For example, thyroidectomy is an appropriate treatment for some forms of hyperthroidism and not for others. Additionally, beta blockers, if not contraindicated, may be used in almost all forms of thyrotoxicosis, whereas antithyroid drugs are useful in only some.

Review in this chapter will mainly focus on hyperthyroidism in non-pregnant adult and subclinical hyperthyroidism, thyroid storm and pregnancy related thyroid dysfunction will be discussed separately in other chapters.

Etiology

Graves Disease

Graves disease, named after an Irish surgeon, Robert J. Graves in 1830, is classified as an autoimmune thyroid disorder [3]. In some patients, Graves disease represents a part of more extensive autoimmune processes leading to dysfunction of multiple organs (e.g., polyglandular autoimmune syndromes). Graves disease is also associated with pernicious anemia, vitiligo, type 1 diabetes mellitus, autoimmune adrenal insufficiency, systemic sclerosis, myasthenia gravis, Sjögren syndrome, rheumatoid arthritis, and systemic lupus erythematosus [4].

Epidemiology

In the United States, the prevalence of hyperthyroidism is approximately 1.2 % (0.5 % overt and 0.7 % subclinical); the most common causes include Graves' disease (GD), toxic multinodular goiter (TMNG), and toxic adenoma (TA) [1, 2]. Graves disease is the most common form of hyperthyroidism in the United States, causing approximately 60–80 % of cases of thyrotoxicosis, and in other parts of the world representing 60–90 % of all cases [5]. In the Wickham Study in the United Kingdom, the incidence was reported to be 100–200 cases per 100,000 population per year [6]. The incidence in women in the UK has been reported to be 80 cases 100,000 per year [7]. As with most autoimmune diseases, susceptibility is increased in females. Hyperthyroidism due to Graves disease has a female-to-male ratio of 7–8:1.

The female-to-male ratio for pretibial myxedema is 3.5:1. Only 7 % of patients with localized myxedema have thyroid acropachy. Unlike the other manifestations of Graves disease, the female-to-male ratio for thyroid acropachy is 1:1. Typically, Graves disease is a disease of young women, but it may occur in persons of any age. The typical age range is 20–40 years. Most affected women are aged 30–60 years. 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 [8].

Pathophysiology and Genetic Interplay

In Graves disease, B and T lymphocyte-mediated autoimmunity are known to be directed at 4 well known thyroid antigens: thyroglobulin, thyroid peroxidase, sodium-iodide symporter and the thyrotropin receptor. However, the thyrotropin receptor itself is the primary autoantigen of Graves disease and is responsible for the manifestation of hyperthyroidism. In this disease, the antibody and cell-mediated thyroid antigen-specific immune responses are well defined [9].

The thyroid gland is under continuous stimulation by circulating autoantibodies against the thyrotropin receptor, and pituitary thyrotropin secretion is suppressed because of the increased production of thyroid hormones. The stimulating

activity of thyrotropin receptor antibodies is found mostly in the immunoglobulin G1 subclass. These thyroid-stimulating antibodies cause release of thyroid hormone and thyroglobulin that is mediated by 3,′5′-cyclic adenosine monophosphate (cyclic AMP), and they also stimulate iodine uptake, protein synthesis, and thyroid gland growth. The anti-sodium-iodide symporter, antithyroglobulin, and antithyroid peroxidase antibodies appear to have little role in the etiology of hyperthyroidism in Graves disease. However, they are markers of autoimmune disease against the thyroid. Intrathyroidal lymphocytic infiltration is the initial histologic abnormality in persons with autoimmune thyroid disease and can be correlated with the titer of thyroid antibodies. Besides being the source of autoantigens, the thyroid cells express molecules that mediate T cell adhesion and complement regulation that participate and interact with the immune system. Several autoimmune thyroid disease susceptibility genes have been identified such as CD40, CTLA-4, thyroglobulin, TSH receptor, and PTPN22 [10].

Some of these susceptibility genes are specific to either Graves disease or Hashimoto thyroiditis, while others confer susceptibility to both conditions. The genetic predisposition to thyroid autoimmunity may interact with environmental factors or events to precipitate the onset of Graves disease. Two new susceptibility loci were found: the RNASET2-FGFR1OP-CCR6 region at 6q27 and an intergenic region at 4p14 [11].

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 [12].

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

Other Associated Autoimmune Diseases

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 [13].

Moreover, strong associations of thyroid-stimulating hormone receptor and major histocompatibility complex class II variants with persistently thyroid stimulating hormone receptor autoantibodies (TRAb)-positive Graves disease were found.

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 [11, 14–18].

Boelaert et al investigated the prevalence of and relative risks for coexisting autoimmune diseases in patients with Graves disease (2791 patients) or Hashimoto thyroiditis (495 patients). The authors found coexisting disorders in 9.7 % of patients with Graves disease and in 14.3 % of those with Hashimoto thyroiditis, with rheumatoid arthritis being the most common of these (prevalence = 3.15 % and 4.24 % in Graves disease and Hashimoto thyroiditis, respectively). Relative risks of greater than 10 were found for pernicious anemia, systemic lupus erythematosus, Addison disease, celiac disease, and vitiligo. The authors also reported a tendency for parents of patients with Graves disease or Hashimoto thyroiditis to have a history of hyperthyroidism or hypothyroidism, respectively [19].

Graves Ophthalmopathy

An infiltrative ophthalmopathy accompanies Graves' disease in about 50 % of patients [20]. The underlying pathophysiology of Graves ophthalmopathy (also called Graves 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 [21, 22].

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. Graves disease patients a have higher rate of peripheral blood mononuclear cell conversion into CD34+ fibrocytes compared with healthy controls. These cells may contribute to the pathophysiology of ophthalmopathy by accumulating in orbital tissues and producing inflammatory cytokines, including Tumor Necrosis Factor-alha(TNF-alpha) and Interleukin-6 (IL-6) [23].

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.

Other Causes of Hyperthyroidism

Toxic Multinodular Goiter (Plummer Disease)

Toxic multinodular goiter causes 5 % of the cases of hyperthyroidism in the United States and can be ten times more common in iodine-deficient areas. It typically occurs in patients older than 40 years with a long-standing goiter, and has a more insidious onset than Graves' disease [24].

While the mechanisms underlying the development of nodules are of complex nature, it has become apparent that hyperfunctioning adenomas within multinodular goiters or autonomous areas within euthyroid goiters harbor somatic gain-of-function mutations in the TSH receptor [25–27]. It is noteworthy that the mutations may differ among the adenomas within the same multinodular goiter. This observation is consistent with studies demonstrating distinct clonal origins of different thyroid adenomas within the same multinodular goiter [28]. The development of multinodular goiters had been associated with a D727E germline polymorphism in the TSH receptor, but this finding could not be corroborated in other studies [29–31].

Toxic Adenoma

Toxic adenoma is the cause of 3–5 % of cases of thyrotoxicosis and characterized by autonomously functioning nodules that are found most commonly in younger patients and in iodine-deficient areas [24]. A toxic adenoma is a monoclonal, autonomously functioning thyroid nodule (AFTN) that produces supraphysiological amounts of T4 and/or T3 resulting in suppression of serum TSH. The function of the surrounding normal thyroid tissue is often, but not always, suppressed. Approximately 1 in 10–20 solitary nodules present with hyperthyroidism. The prevalence of hyperthyroidism appears to be more common in Europe than in the USA, and it is more common in women than in men [32, 33]. Chronic stimulation of the cAMP cascade results in enhanced proliferation and function of thyrocytes [33]. Hence, any molecular alteration leading to constitutive activation of the cAMP pathway in a thyroid follicular cell is expected to result in clonal autonomous growth and function, and ultimately in a toxic adenoma [34]. In line with this concept, somatic mutations were first discovered in the *GNAS1* gene encoding the stimulatory Gs alpha subunit in toxic adenomas [34–36]. Stimulatory Gs alph amutations impair the hydrolysis of guanine triphosphate (GTP) to guanine diphosphate (GDP), resulting in persistent activation of adenylyl cyclase. The reported prevalence of TSH receptor mutations in toxic adenomas varies widely, but is as high as 80 % [35, 36].

It is now well established that somatic, constitutively activating TSH receptor mutations play a predominant role in the pathogenesis of AFTNs, while Gs alpha mutations are less common [37]. It is likely that other somatic mutations are involved in the pathogenesis of the monoclonal

toxic adenomas that are negative for mutations in the TSH receptor and Gs alpha [38].

Thyroiditis

Subacute: Subacute thyroiditis produces an abrupt onset of thyrotoxic symptoms as hormone leaks from an inflamed gland. It often follows a viral illness. Symptoms usually resolve within 8 months. This condition can be recurrent in some patients [39].

Lymphocytic and Postpartum: Lymphocytic Thyroiditis and postpartum (subacute lymphocytic) thyroiditis are transient inflammatory causes of hyperthyroidism that, in the acute stage, may be clinically indistinguishable from Graves' disease. Postpartum thyroiditis can occur in up to 5–10 % of women in the first 3–6 months after delivery. A transient hypothyroidism often occurs before resolution [39].

Hashimoto's Thyroiditis: Occasionally, Hashimoto's thyroiditis is accompanied by mild symptoms of thyrotoxicosis, particularly in the early phases of the disease [40]. A detailed description of thyroiditis is provided in Chap. 6.

Drug-Induced Hyperthyroidism

Iodine-Induced: Iodine-induced hyperthyroidism can occur after intake of excess iodine in the diet, exposure to radiographic contrast media, or medications. Excess iodine increases the synthesis and release of thyroid hormone in iodine-deficient patients and in older patients with preexisting multinodular goiters [41].

Amiodarone-Induced: Amiodarone induced hyperthyroidism can be found in up to 12 % of treated patients, especially those in iodine-deficient areas, and occurs by two mechanisms. Because amiodarone contains 37 % iodine, type I is an iodine induced hyperthyroidism (see above). Amiodarone is the most common source of iodine excess in the United States. Type II is a thyroiditis that occurs in patients with normal thyroid glands. Medications such as interferon and interleukin- 2 (aldesleukin) also can cause type II Thyroiditis [41].

Thyroid Hormone-Induced: Factitious hyperthyroidism is caused by the intentional or accidental ingestion of excess amounts of thyroid hormone. Some patients may take thyroid preparations to achieve weight loss.

Tumors Induced Hyperthyroidism

Rare causes of hyperthyroidism include metastatic thyroid cancer, ovarian tumors that produce thyroid hormone (struma ovarii), trophoblastic tumors that produce human chorionic gonadotrophin and activate highly sensitive TSH receptors.

TSH-Secreting Pituitary Adenoma

TSH-secreting adenomas (TSHomas) account for less than 2 % of all pituitary adenomas and are a rare cause of thyrotoxicosis [42, 43]. The molecular mechanisms leading to the formation of TSHomas remain unknown. TSHomas have been shown to be monoclonal by X-inactivation analyses suggesting that they arise from a single cell harboring one or several mutations in genes controlling proliferation and perhaps function.

Hyperthyroidism Secondary to Thyroid Hormone Resistance

The syndrome of Resistance to Thyroid Hormone (RTH) is defined by elevated circulating levels of free thyroid hormones due to reduced target tissue responsiveness and normal, or elevated levels of TSH [44, 45].

Patients with RTH typically present with goiter. Their metabolic state may appear euthyroid or include signs of hypo- and hyperthyroidism. RTH is most commonly caused by monoallelic mutations of the *TRbeta* gene. The mutation can be inherited in an autosomal dominant manner or occur as *de novo* mutation.

Hyperthyroidism due to TSH-Receptor Mutations

Autosomal dominant familial hyperthyroidism without evidence of an autoimmune etiology has been first described by Thomas et al. in 1982.

Currently 27 families with a total of 152 affected individuals with non-autoimmune familial hyperthyroidism have been reported . The hyperthyroidism is caused by monoallelic gain-of-function germline mutations in the TSH receptor [46, 47].

Affected individuals have a suppressed TSH and elevated peripheral hormones in the absence of TSH receptor-stimulating antibodies and TPO antibodies. The family history is key in order to demonstrate familial clustering suggestive for an autosomal dominant disorder. Ultimately, the diagnosis requires sequence analysis of the *TSH receptor* gene in order to evaluate it for the presence of a monalllelic mutation.

Clinical Features

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.

The family history should include careful evaluation of the autoimmune disease, thyroid disease and emigration from iodine-deficient parts of the world. Health care provider should also review a complete list of medications and dietary supplements. A number of compounds—including expectorants, amiodarone, iodinated contrast agents, and health food supplements containing seaweed or thyroid gland extracts—contain large amounts of iodine that can induce hyperthyroidism in a patient with thyroid autonomy. Rarely, iodine exposure can cause hyperthyroidism in a patient with an apparently healthy thyroid. Hyperthyroidism presents with multiple symptoms that vary according to the age of the patient, duration of illness, magnitude of hormone excess, and presence of comorbid conditions. Symptoms are related to the thyroid hormone's stimulation of catabolic enzymopathic activity and catabolism, and enhancement of sensitivity to catecholamines. Older patients often present with a paucity of classic signs and symptoms, which can make the diagnosis more difficult [41, 48].

Hyperthyroidism leads to an apparent increase in sympathetic nervous system. 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 [37, 49].

The clinical manifestations of hyperthyroidism do not always correlate with the extent of the biochemical abnormality.

Common symptoms of hyperthyroidism include the following:

- Nervousness
- Insomnia
- Anxiety
- Increased perspiration
- Heat intolerance
- Hyperactivity
- Palpitations
- Weight loss despite increased appetite.
- Hyperdefecation
- Reduction in menstrual flow or oligomenorrhea

Common signs of hyperthyroidism include the following:

- Diffuse goiter/toxic nodule/multinodular goiter
- Exophthalmos
- Tachycardia or atrial arrhythmia
- Systolic hypertension
- Warm, moist, smooth skin
- Lid lag
- Stare
- Hand tremor
- Proximal myopathy
- Brisk deep tendon reflexes

Features pathognomonic of Graves' disease include the following:

- Orbitopathy
- Thyroid bruit
- Pretibial myxedema
- Acropachy

Features of Graves Ophthalmopathy
Approximately 50 % of patients with Graves thy-

rotoxicosis 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 . Evidence of thyroid eye disease and high thyroid hormone levels confirms the diagnosis of autoimmune Grave disease.

Graves Dermopathy 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.

Features Related to Other Causes of Hyperthyroidism

Toxic adenomas present with signs and symptoms of hyperthyroidism and/or a thyroid nodule. The signs and symptoms of thyrotoxicosis do not differ from other etiologies. Features suggestive for Graves' disease such as endocrine ophthalmopathy, (pretibial) myxedema and acropachy are missing. The onset of hyperthyroidism is often insidious and more common in older patients, who typically have larger adenomas. Mechanical symptoms such as dysphagia or hoarseness are uncommon. Autonomously functioning nodules may remain stable in size, grow, degenerate or become gradually toxic. In one series, 10 % of patients followed for 6 years became thyrotoxic [32]. Thyrotoxicosis may develop independent of age, but is much more common in nodules over 3 cm in diameter (up to 20 %).

Toxic Multinodular Goiter In addition to the signs and symptoms associated with hyperthyroidism, patients with large toxic multinodular goiters may also have dysphagia, shortness of breath, stridor, or hoarseness.

Subacute thyroiditis often present with a history of a preceding respiratory tract infection [50]. They may have fever, malaise, and soreness, and the gland is exquisitely tender on palpation and often displays a substantially increased consistency.

Hydatiform Moles and Choriocarcinoma Most women with hydatiform moles present with uterine bleeding in the first half of pregnancy. The size of the uterus is large for the duration of gestation [51].

Many women with molar pregnancies have nausea and vomiting, some have pregnancy-induced hypertension or pre-eclampsia. The signs and symptoms of thyrotoxicosis are present in some women, but they may be obscured by toxemic signs. The characteristic features belonging to Graves' disease are missing. Hyperthyroidism is usually not severe because of a relatively short duration.

Women with choriocarcinomas present within 1 year after conception. The tumor may be confined to the uterus, more frequently it is metastatic to multiple organs such as the liver and lungs. In men, choriocarcinomas of the testes is often widely metastatic at initial presentation. Gynecomastia is a common finding.

Struma Ovarii The clinical presentation may include the finding of an abdominal mass, ascites, pelvic pain, and, rarely, a pseudo-Meigs syndrome with pleural effusions. A subset of women present with subclinical or overt thyrotoxicosis. Goiter is only presented in patients with associated thyroid disease. For example, coexistence of Graves' disease and struma ovarii has been reported [52, 53].

Apathetic Hyperthyroidism

Hyperthyroidism in the elderly is a great masquerader, and even severe, life-threatening hyperthyroidism can easily be missed in patients older than 60 years [54]. Not uncommonly, it appears in an atypical manner, and the classic symptoms are often absent. Graves disease and toxic multinodular goiter account for most cases in the elderly, while as Solitary toxic adenomas are rare in elder patients [55–58]. Again, like hypothyroidism, the

symptoms of hyperthyroidism are often atypical and may mimic other common diseases in this age group. They may be absent, subtle, or may be obscured by coexisting diseases. Cardiac complications are the most common manifestations of hyperthyroidism in elderly. They are usually manifested as atrial arrhythmias (commonly atrial fibrillation with slow ventricular rates, as compared with high rates in young patients); congestive heart failure (usually high output heart failure) and angina pectoris. The underlying hyperthyroidism may not be recognized, since older patients usually do not show the classic signs/symptoms of thyroid overactivity [59]. Rather than increased appetite, weight loss with anorexia may be present. Diarrhea is common in young hyperthyroid patients; elderly patients may note a correction of preexisting constipation but will rarely complain of loose stools. Elderly patients can present with only one symptom of hyperthyroidism, sometimes referred to as monosymptomatic hyperthyroidism. Agitation and confusion can also be presenting symptoms [60].

Diagnostic Modalities

Hormonal Assays

Serum TSH The measurement of serum TSH with a sensitive third-generation assay represents the best biochemical marker to establish the diagnosis of hyperthyroidism because TSH and FT4 have an inverse log-linear relationship and a small decrease or increase in FT4 is thus associated with an exponential change in TSH levels [61].

Although measurement of the TSH level is the most reliable screening method for assessing thyroid function, the degree of hyperthyroidism cannot be estimated easily in this way. Instead, hyperthyroidism 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 thyroxin binding prealbumin, and albumin).

Free T4 (FT4) and free T3 measurement is recommended in patients with suspected hyperthyroidism when TSH is low. Many laboratories do not measure FT4 directly, instead using a calculation to estimate the FT4 level. Serum free T4 can be estimated by several different methods such as equilibrium dialysis techniques or estimated indirectly by calculation of the free-thyroxine index (FTI):

Free-thyroxine index (FTI)
= Total $T_4 \times T_3$ resin uptake (T_3RU) %.

The T3 resin uptake (T3RU) test indirectly estimates unsaturated binding sites on thyroid binding globulin (TBG). The patient's serum is incubated with radiolabelled T3 tracer. The unbound tracer is trapped with resin, and the value is reported as percent tracer uptake by resin. The greater the number of free TBG-binding sites, the lower the uptake of tracer by the resin. The normal range for T3RU is between 25 % and 35 %.

Since Free thyroxine (FT4) and free triiodothyronine (FT3) assays now available in most of the laboratories, therefore, FTI and T3 resin uptake measurement are rarely required.

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.

Antibodies

Anti Thyroid Peroxidase(TPO) Antibody The most specific autoantibody test for autoimmune thyroiditis is an ELISA test for anti-Thyroid Peroxidase(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.

Although, antithyroid antibodies are elevated in Graves' disease and lymphocytic thyroiditis but usually are not necessary to make the diagnosis [62].

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 Thyroid stimulating immunoglobulins, also known as TSIs, are autoantibodies that are produced by the immune system in the setting of Graves' disease. Antibodies are molecules produced by white blood cells called B cells. B cells are stimulated to produce antibodies through a series of interactions with other white blood cells called helper T cells. These interactions transform B cells into plasma cells that secrete large amounts of antibodies. TSIs are somewhat unique in that they do not directly promote the destruction of any normal cells or structures in the thyroid gland. Instead they mimic the action of TSH itself, driving the TSH receptors to generate signals that stimulate the production and secretion of thyroid hormone. This process is not governed by the normal feedback mechanism that regulates the secretion of TSH from the pituitary gland. As such, TSIs that bind to TSH receptors may stimulate the production and secretion of excess amounts of thyroid hormone.

Elevated TSIs help to establish the diagnosis of Graves's disease. Thyroid-stimulating antibody levels can be used to monitor the effects of treatment with antithyroid drugs in patients with Graves' disease [63]. Circulating antithyroglobulin (anti-TG) antibodies are also present in Graves disease; however, testing for these antibodies should not be helpful, because anti-TG antibodies may be present in persons without evidence of thyroid dysfunction [64]. A high titer of serum antibodies to collagen XIII is associated with active Graves ophthalmopathy [65].

Other Relevant Investigations

Nonspecific laboratory findings can occur in hyperthyroidism, including anemia, granulocytosis, lymphocytosis, hypercalcemia, transaminase elevations, and alkaline phosphatase elevation [41].

Liver function test results should be obtained to monitor for liver toxicity caused by thioamides (antithyroid medications). A complete blood count (CBC) with differential should be obtained at baseline and with the development of fever or symptoms of infection. Graves disease may be associated with normocytic anemia, low-normal to slightly depressed total WBC count with relative lymphocytosis and monocytosis, low-normal to slightly depressed platelet count. Thionamides may rarely cause severe hematologic side effects, but routine screening for these rare events is not cost-effective.

Investigation of gynecomastia associated with Graves disease may reveal increased sex hormone–binding globulin levels and decreased free testosterone levels.

Hyperthyroidism may worsen diabetes control and may be reflected by an increase in hemoglobin A1C in diabetic patients.

A fasting lipid profile may show decreased total cholesterol levels and decreased triglyceride levels.

Measurement of serum hCG concentrations is needed for the diagnosis of moles and choriocarcinomas, and hCG serves as a sensitive and specific tumor marker during therapy and surveillance. In women, hCG concentrations are significantly higher than those found during normal pregnancies. CA125 may be found to be elevated in ovarian cancer.

Ultrasound

Ultrasounds with color-doppler evaluation have been found to be cost-effective in hyperthyroid patients and can differentiate between solitary adenoma and multinodular goiter [66, 67].

A prospective trial showed that thyroid ultrasound findings are predictive of radioiodine treatment outcome, and, in patients with

Graves disease, normoechogenic and large glands are associated with increased radioresistance [67].

In Graves disease ultrasound often shows a diffusely enlarged thyroid gland and is often hyperechoic and of heterogeneous echotexture. There is relative absence of nodularity in uncomplicated cases. Gland may become hypervascular and demonstrate a "thyroid inferno" pattern on color doppler [68]. Ultrasound will confirm the presence of a solitary nodule, adenoma and multinodular goiter. There is no indication to perform fine needle aspiration in patients with toxic adenomas because the risk of a thyroid carcinoma is extremely low and cytological evaluation will not permit distinguishing between a follicular adenoma and a follicular carcinoma [69].

Radioisotope Thyroid Scan

If the etiology of hyperthyroidism is not clear after physical examination and other laboratory tests, it can be confirmed by means of scintigraphy. A thyroid scan can be performed with 123iodine, 131iodine, or 99technetium-labeled pertechnetate . Normally, the isotope distributes homogeneously throughout both lobes of the thyroid gland. In patients with hyperthyroidism, the pattern of uptake (e.g., 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.

Scintigraphically, an adenoma may be warm (uptake similar to surrounding tissue), hot (uptake increased without suppression of surrounding tissue), or toxic (uptake increased and suppression of the surrounding tissue).

Radioisotope Findings

Radionuclide uptake and scan easily distinguishes the high uptake of Graves' disease from the low uptake of thyroiditis and provides other useful anatomic information.

Following characterizes the radioisotope findings of common causes of hyperthyroidism : (see Table 8.1)

- 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.
- Toxic adenoma- Increased tracer uptake.
- Subacute thyroiditis –Very low radioactive iodine uptake.

MRI/CT Scan

Computed tomography scanning or magnetic resonance imaging (of the orbits) may be necessary in the evaluation of proptosis. If routinely performed, most patients have evidence of orbitopathy, such as an increased volume of extraocular muscles and/or retrobulbar connective tissue. These tech-

Table 8.1 Radiotracer uptake in hyperthyroidism

Causes	24 h radioactive iodine uptake
Graves disease	Increased (moderate to high: 40–100 %)
Toxic adenoma	Increased (mild to moderate: 25–60 %)
Toxic multinodular goiter	Increased (mild to moderate: 25–60 %)
Subacute thyroiditis	Decreased (very low: <2 %)
Iodide-induced hyperthyroidism	Variable but usually low (<25 %)
Thyrotoxicosis factitia	Decreased (very low: <2 %)
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 %)
Struma ovarii with hyperthyroidism	Decreased

niques are useful to monitor changes over time or to ascertain the effects of treatment. Careful monitoring is required after using iodinated contrast agents as they may affect ongoing treatment plans. The diagnostic approach is in general similar to patients with a solitary AFTN, but cross-sectional imaging with computer tomography and pulmonary function tests need to be considered in a subset of patients in whom compression by the goiter is evident or suspected MRI pituitary may be required in ascertaining pituitary TSHoma. Cross-sectional imaging with computed tomography or magnetic resonance imaging will demonstrate uni- or bilateral ovarian masses in struma ovarii.

Treatment

If left untreated hyperthyroidism can cause thyrotoxic storm and long-standing severe thyrotoxicosis leads to severe weight loss with catabolism of bone and muscle [70].

The treatment of hyperthyroidism depends on the cause and severity of the disease, as well as on the patient's age, goiter size, comorbid conditions, and patient's preference.

The goal of therapy is to correct the hypermetabolic state with the fewest side effects and the lowest incidence of hypothyroidism. Beta blockers and iodides are used as treatment adjuncts. Antithyroid drugs, radioactive iodine, and surgery are the main treatment options for persistent hyperthyroidism [5, 20, 41, 62]. See Table 8.2.

Each therapy can produce satisfactory outcomes if properly used [71].

Following is the detailed description of therapy.

Symptomatic Relief

Beta Blockers Many of the neurologic and cardiovascular symptoms of hyperthyroidism are relieved by beta-blocker s. 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 or heart failure.

Beta blockers offer prompt relief of the adrenergic symptoms of hyperthyroidism such as tremor, palpitations, heat intolerance, and nervousness. Propranolol (Inderal) has been used most widely, but other beta blockers can be used. Nonselective beta blockers such as propranolol, are preferred because they have a more direct effect on hypermetabolism [72]. Therapy with propranolol should be initiated at 10–20 mg every 6 h. The dose should be increased progressively until symptoms are controlled. In most cases, a dosage of 80–320 mg per day is sufficient [41].

Calcium Channel Blockers (e.g., 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.

Calcium channel blockers such as diltiazem can be used to reduce heart rate in patients who cannot tolerate beta blockers [73].

Table 8.2 Treatment modalities: Pros and cons

Treatment modalities	Pros	Cons
Thioamide drug therapy	Avoiding surgery and radioactive ablation therapy	Adverse drug effects
	Less chances of life long thyroxine replacement	
131I Ablation therapy	Definitive therapy	Worsening of Graves ophthalmopathy
	Avoiding surgical risk	Life long thyroxine replacement
		Radiation exposure
		Contraindicated in pregnancy
Surgical intervention	Rapid resolution	Risk related to surgery
		Life long thyroxine replacement

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.

Antithyroid Medications

Thioamides (Cabimazole, methimazole and propylthiouracil) act principally by interfering with the organification of iodine, thereby suppressing thyroid hormone levels. Remission rates vary with the length of treatment, but rates of 60 % have been reported when therapy is continued for 2 years [63].

Relapse can occur in up to 50 % of patients who respond initially, regardless of the regimen used. A recent randomized trial indicated that relapse was more likely in patients who smoked, had large goiters, or had elevated thyroid-stimulating antibody levels at the end of therapy [74].

Methimazole and carbimazole are the antithyroid drugs most frequently used both for the preoperative and long-term medical management of hyperthyroidism because of their consistent and potent effect on lowering thyroid hormone concentrations. Both drugs are actively concentrated by the thyroid gland where they exert their effect by inhibiting thyroid hormone production. Carbimazole is actually converted to methimazole such that only methimazole accumulates in the thyroid gland. This conversion results in a 5 mg dose of carbimazole being approximately equivalent to 3 mg of methimazole (reflecting the molar ratio of the two drugs). Methimazole is available as both human and veterinary formulations (2.5 and 5 mg). Carbimazole is only available as a preparation for human use. Carbimazole/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 (i.e., toxic multinodular goiter and toxic adenoma) are permanent conditions and will not go into remission [75].

Cabimazole/Methimazole Generally is the drug of choice in nonpregnant patients because of its lower cost, longer half-life, and lower incidence of hematologic side effects. The starting dosage is 15–30 mg per day (60 mg is the maximum dose) and it can be given in conjunction with a beta blocker [76].

Methimazole is more potent than propylthiouracil and has a longer duration of action. In addition, methimazole is taken once daily, patient compliance is often better with methimazole than with propylthiouracil. Methimazole is not recom-

mended 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 [77, 78].

The beta blockade can be tapered after 4–8 weeks and the methimazole adjusted, according to clinical status and monthly free T4 or free T3 levels, toward an eventual maintenance dosage of 5–10 mg per day [20, 73].

TSH levels may remain undetectable for months after the patient becomes euthyroid and should not be used to monitor the effects of therapy. At 1 year, if the patient is clinically and biochemically Euthyroid and a thyroid-stimulating antibody level is not detectable, therapy can be discontinued. If the thyroid-stimulating antibody level is elevated, continuation of therapy for another year should be considered. Once antithyroid drug therapy is discontinued, the patient should be monitored every 3 months for the first year, because relapse is more likely to occur during this time, and then annually, because relapse can occur years later. If relapse occurs, radioactive iodine or surgery generally is recommended, although antithyroid drug therapy can be restarted [20].

Propylthiouracil PTU is preferred for pregnant women because methimazole has been associated with rare congenital abnormalities. The starting dosage of PTU is 100 mg three times per day (maximum dose is 600 mg/day) with a maintenance dosage of 100–200 mg daily in two to three divided doses [76].

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 carbimazole or methimazole. Propylthiouracil remains the drug of choice in uncommon situations of life-threatening severe thyrotoxicosis (i.e., thyroid storm) because of the additional benefit of inhibition of T4 -to-T3 conversion. In this setting, propylthiouracil should be administered every 6–8 h. 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.

Adverse Effects of Thioamide Antithyroid Medications

The most common adverse effects of thioamide 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. Agranulocytosis is the most serious adverse reaction of antithyroid drug therapy and is estimated to occur in 0.1–0.5 % of patients treated with these drugs [76].

The risk is higher in the first several months of therapy and may be higher with PTU than methimazole [20, 41, 63]. The onset of agranulocytosis is sometimes abrupt, so patients should be warned to stop taking the drug immediately if they develop a sudden fever or sore throat. 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 most cases, agranulocytosis is reversible with supportive treatment [63, 72].

Routine monitoring of white cell counts remains controversial, but results of one study showed that close monitoring of white cell counts allowed for earlier detection of agranulocytosis. In this study, patients had white cell counts every 2 weeks for the first 2 months, then monthly [79].

Minor side effects (e.g., rash, fever, gastrointestinal symptoms) sometimes can be treated symptomatically without discontinuation of the antithyroid drug; however, if symptoms of arthralgia occur, antithyroid drugs should be discontinued because arthralgia can be a precursor of a more serious polyarthritis syndrome. Other serious adverse effects include aplastic anemia, hepatitis, polyarthritis, and a lupus like vasculitis.

The FDA recommends the following measures for patients receiving propylthiouracil [80]:

- 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.

Radioactive Iodine 131 Ablation (RAI^{131})

Radioactive iodine therapy is the most common treatment for Graves disease and toxic multinodular goiter in adults in the United States [81].

In Europe and Japan, there has been a greater physician preference for ATDs and/or surgery [82]. Although its effect is less rapid than that of antithyroid medication or thyroidectomy, it is effective and safe and does not require hospitalization.

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.

Radioactive iodine therapy for TMNG results in resolution of hyperthyroidism in approximately 55 % of patients at 3 months and 80 % of patients at 6 months, with an average failure rate of 15 % [83–85]. Goiter volume is decreased by 3 months, with further reduction observed over 24 months, for a total size reduction of 40 %. Generally, the dose of ^{131} I administered is 75–200 μCi/g of estimated thyroid tissue divided by the percent of 123 I uptake in 24 h. 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 h), 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 [86].

There is also no evidence that radioactive iodine therapy for hyperthyroidism results in increased mortality for any other form of cancer, including leukemia [87].

Long-term follow-up data of children and adolescents treated with radioactive iodine are lacking [62, 63].

American Thyroid Association (ATA) guidelines recommend avoiding^{131} I therapy in children younger than 5 years of age. In children 5–10 years old, ^{131} I therapy is acceptable if the calculated activity of administered^{131} I 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 [88].

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 [89]. This worsening is usually mild but occasionally severe. 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. See algorithm for steroid treatment in Graves ophthalmopathy.

Using antithyroid drugs to achieve a euthyroid state before treatment with radioactive iodine is not recommended for most patients, but it may improve safety for patients with severe or complicated hyperthyroidism. It is unclear whether antithyroid drugs increase radioactive iodine failure rates [5, 90–92].

If used, they should be withdrawn at least 3 days before radioactive iodine and can be restarted 2–3 days later. The antithyroid drug is continued for 3 months after radioactive iodine, and then tapered.

Most of the radioactive iodine is eliminated from the body in urine, saliva, and feces within 48 h; however, double flushing of the toilet and frequent hand washing are recommended for several weeks. Close contact with others, especially children and pregnant women, should be avoided for 24–72 h [93].

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 [94].

Other Less Commonly Used Antithyroid Medications

Iodides Iodides block the peripheral conversion of thyroxine (T4) to triiodothyronine (T3) and inhibit hormone release. Iodides also are used as adjunctive therapy before emergency nonthyroid surgery, if beta blockers are unable to control the hyperthyroidism, and to reduce gland vascularity before surgery for Graves' disease [20].

Iodides are not used in the routine treatment of hyperthyroidism because of paradoxical increases in hormone release that can occur with prolonged use. Organic iodide radiographic contrast agents (e.g., iopanoic acid or ipodate sodium) are used more commonly than the inorganic iodides (e.g., potassium iodide). The dosage of either agent is 1 g per day for up to 12 weeks [95].

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.

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).

Bile Salt Sequestrant 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 g in 3 divided daily doses have been used for 4 weeks.

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 [81, 96].

Indications for Thyroidectomy

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:

- Large goiter with compressive symptoms
- Pregnant women who are noncompliant with or intolerant of antithyroid drugs
- Patients who refuse radioactive iodine therapy and antithyroid treatment
- Failure to medical treatment
- Goiter with malignant potential

Preparation for Thyroidectomy

Preparation for thyroidectomy includes antithyroid medication, iodine treatment and beta-blocker therapy [96].

In severe hyperthyroidism, 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 [97].

Adverse Effects of Thyroidectomy

During the 1800s, the mortality rate from thyroid surgery was approximately 40 %. Most deaths were caused by infection and hemorrhage [98].

Sterile surgical arenas, general anesthesia, and improved surgical techniques have made death from thyroid surgery extremely rare today. With current operative techniques, bilateral subtotal thyroidectomy should have a mortality approaching zero in patients who are properly prepared. Adverse effects of thyroidectomy include:

Postoperative Bleeding

The incidence of bleeding after thyroid surgery is low (0.3–1 %), but an unrecognized or rapidly expanding hematoma can cause airway compromise and asphyxiation [99].

Infection

Currently, postoperative infection occurs in less than 1–2 % of all thyroid surgery cases. Sterile surgical technique is the key to prevention [100];

Injury to the Recurrent Laryngeal Nerve

Recurrent laryngeal nerve (RLN) injury results in true vocal-fold paresis or paralysis. Deliberate intraoperative identification and preservation of the RLN minimizes the risk of injury [101].

Injury to the Superior Laryngeal Nerve

The external branch of the superior laryngeal nerve (SLN) is probably the nerve most commonly injured in thyroid surgery, with an injury rate estimated at 0–25 %. Trauma to the nerve results in an inability to lengthen a vocal fold and, thus, inability to create a high-pitched sound; this may be career-threatening for singers or others who rely on their voice for their profession [102].

Hypoparathyroidism

Hypoparathyroidism can result from direct trauma to the parathyroid glands, devascularization of the glands, or removal of the glands during surgery. Postoperative hypoparathyroidism, and the resulting hypocalcemia, may be permanent or transient. Hypocalcemia after thyroidectomy is initially asymptomatic in most cases [103].

Hypothyroidism

Hypothyroidism is an expected consequence of total thyroidectomy and measurement of TSH levels is the most useful laboratory test for detecting or monitoring of hypothyroidism in these patients [104].

Thyrotoxic Storm

Thyrotoxic storm is an unusual complication that may result from manipulation of the thyroid gland during surgery in patients with hyperthyroidism. It can develop intraoperatively, or postoperatively [104]. A detailed account of this entity is given in Chap. 12

Follow up After Thyroid Surgery

Patients whose thyroid functions normalize after surgery require routine follow-up because hypothyroidism, 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 (Throxine 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 thyroxine dosage should be adjusted to maintain a normal TSH level.

Cause-Specific Treatment

Transsphenoidal surgeries, in combination with radiotherapy and somatostatin analogues in some patients with pituitary adenoma (TSHoma) are the treatment options. Hydatiform moles are treated by suction. Choriocarcinomas can be treated successfully in most patients with chemotherapy. Most patients with struma ovarii are clinically and biochemically euthyroid. Unilateral or bilateral open or laparoscopic oophorectomy is the primary therapy [105].

Thyrotoxic women with struma ovarii should be treated with antithyroid drugs and, if needed, with beta-blockers prior to surgery. In the case of malignant lesions, the patient should undergo thyroidectomy followed by treatment with 131iodine [106].

Future Directions

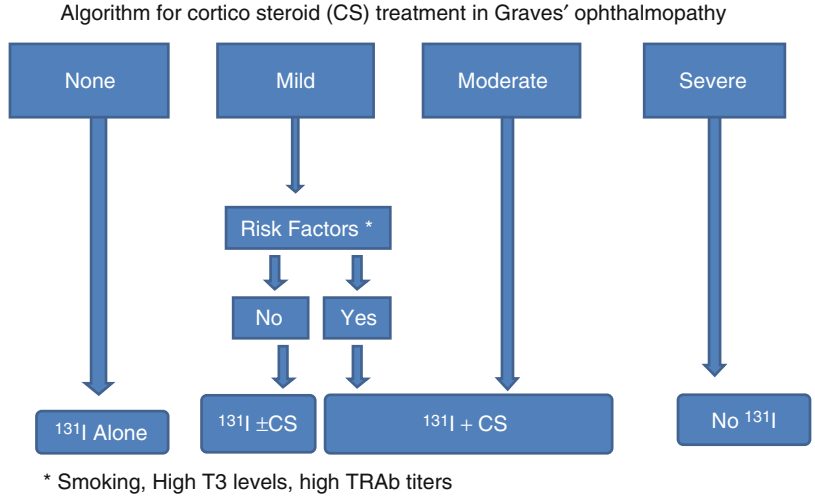
A promising new drug for the treatment of Graves ophthalmopathy is rituximab, an anti-CD20 monoclonal antibody causing depletion of CD20-positive B cells and thereby initially used for CD20-positive non-Hodgkin's lymphomas. Rituximab has then also been employed for several autoimmune disorders, both T cell and B cell driven. Data are too preliminary to draw any definite conclusion [107]. Other newer treatment options include endoscopic subtotal thyroidectomy [108], embolization of the thyroid arteries [109], plasmapheresis [110], and percutaneous ethanol injection of toxic thyroid nodules [111]. Autotransplantation of cryopreserved thyroid tissue may become a treatment option for postoperative hypothyroidism [112]. Nutritional supplementation with L-carnitine [113] has been shown to have a beneficial effect on the symptoms of hyperthyroidism, and L-carnitine may help prevent bone demineralization caused by the disease.

Conclusion

Hyperthyroidism has a broad spectrum of etiologies, clinical manifestations and carries significant morbidity and mortality, if left untreated. While it is most commonly caused by Graves' disease, it is of importance to recognize other etiologies in order to choose the most appropriate therapeutic option and long-term surveillance. Toxic adenomas are characterized by a single hyperactive nodule in the thyroid leading to clinical and biochemical hyperthyroidism. Older patients with a hot nodule are more likely to become toxic as compared to younger patients. The likelihood of malignancy in a toxic nodule is very low. In multinodular goiters, several nodules display an autonomous function. Administration of moderate or high doses of iodine may induce hyperthyroidism in patients with or without

apparent pre-existing thyroid disease. An antiarrhythmic drug amiodarone, which may induce hyperthyroidism because of its high iodine content and/or a drug-induced thyroiditis. Any form of thyroiditis can be associated with a thyrotoxic phase because the disruption of thyroid follicles can result in an increased release of stored iodothyronines. The thyrotoxic phase may be followed by transient or permanent hypothyroidism. Hyperthyroidism in elderly may easily be missed because of atypical presentation and a high index of suspicion is required to timely diagnose and treat this life threatening condition in elderly.

Graves' disease, toxic multinodular goiter, and toxic adenoma can be treated with radioactive iodine, antithyroid drugs, or surgery. Thyroidectomy is an option when other treatments fail or are contraindicated, or when a goiter is causing compressive symptoms. Special treatment consideration must be given to patients who are pregnant or breastfeeding, as well as those with Graves' ophthalmopathy. Patients' desires must be considered when deciding on appropriate therapy, and close monitoring and follow up for disease status and drug side effects are essential components of management.



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