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Hyperthyroidism:

A Review

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Abstract

Importance: Overt hyperthyroidism, defined as suppressed thyrotropin (TSH) and high triiodothyronine (T3) and/or free thyroxine (FT4) levels, affects approximately 0.2-1.4% of people worldwide. Subclinical hyperthyroidism, defined as low TSH and normal T3 and FT4 levels, affects approximately 0.7-1.4% of people worldwide. Untreated hyperthyroidism can cause cardiac arrhythmias, heart failure, osteoporosis, adverse pregnancy outcomes, and metabolic abnormalities leading to unintentional weight loss, and is associated with increased mortality.

Observations: The most common cause of hyperthyroidism is Graves' disease, with a global prevalence of 2% in women and 0.5% in men. Other causes of hyperthyroidism and thyrotoxicosis include toxic nodules and the thyrotoxic phase of thyroiditis. Common symptoms of thyrotoxicosis include anxiety, insomnia, palpitations, unintentional weight loss, diarrhea, and heat intolerance. Patients with Graves' disease may have diffusely enlarged thyroid glands, stare, or exophthalmos on exam. Patients with toxic nodules may have symptoms from local compression of structures in the neck by the thyroid gland, such as dysphagia, orthopnea, or voice changes. Etiology can typically be established based on clinical presentation, thyroid function tests, and TSH-receptor antibody status. Thyroid scintigraphy is recommended if thyroid nodules are present, or the etiology is unclear. Thyrotoxicosis from thyroiditis may be observed or treated with supportive care. Treatment options for overt hyperthyroidism from autonomous thyroid nodules or Graves' disease include antithyroid drugs (ATD), radioactive iodine (RAI) ablation, and

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surgery. Treatment for subclinical hyperthyroidism is recommended for patients at highest risk for osteoporosis and cardiovascular disease, such as those >60 years or age, or with serum TSH level < 0.1mIU/L on multiple occasions.

Conclusions and Relevance: Hyperthyroidism affects 2.5% of adults worldwide and is associated with osteoporosis, heart disease, and increased mortality. First-line treatments are antithyroid drugs, thyroid surgery, and RAI treatment. Treatment choices should be individualized and patient-centered.

Introduction

The global prevalence of hyperthyroidism in iodine-sufficient countries is estimated at 0.2-2.5%.[1] The prevalence of overt hyperthyroidism, defined as low thyroid stimulating hormone [TSH] with elevated triiodothyronine [T3] and/or free thyroxine [T4], is approximately 0.2-1.4%. The prevalence of subclinical hyperthyroidism, defined as low TSH with normal peripheral thyroid hormone, is approximately 0.7-1.4%.[1,2] Thyrotoxicosis refers to all conditions in which thyroid hormone levels are elevated, regardless of underlying mechanism.[3] Thyrotoxicosis may occur due to hyperthyroidism from increased thyroid hormone production, release of preformed hormones from the thyroid gland due to inflammation, or extrathyroidal thyroid hormone availability due to excess T4 repletion, surreptitious thyroid hormone ingestion, or struma ovarii. Struma ovarii is a type of dermoid tumor of the ovary, in which thyroid tissue is the predominant component of the tumor. Untreated hyperthyroidism can cause cardiac arrhythmias, congestive heart failure, osteoporosis, adverse obstetric outcomes, and metabolic derangements such as increased resting energy expenditure and gluconeogenesis.[3]

This review summarizes current evidence regarding the pathophysiology, clinical presentation, and treatment of hyperthyroidism, focusing on the management of Graves' disease and toxic nodular disease.

Methods

We searched PubMed for English-language studies published from June 2013 through June 26, 2023, including the most up-to-date information for the terms "thyrotoxicosis and "hyperthyroidism." We included randomized clinical trials (RCTs), meta-analyses, systematic reviews, and observational studies. Current practice guidelines were also reviewed. We manually searched the references of selected articles, reviews, meta-analyses, and guidelines. 2,185 papers were retrieved from the initial search. Of these, 108 were included for this review (4 randomized clinical trials, 21 systematic review or meta-analyses, 40 longitudinal prospective or retrospective observational studies, 2 cross-sectional studies, and 41 reviews). Articles were selected based on quality of the study design, recency of data, and relevance to general medical practice.

Pathophysiology

Graves disease is an autoimmune disease, in which autoantibodies directed against the thyroidal TSH receptor cause increased thyroid hormone synthesis and secretion. Graves

disease is the most common cause of hyperthyroidism in iodine-replete populations, with a prevalence of 2% in women and 0.5% in men (Table 1).[1,4] Thyroid nodules with somatic activating variants in genes that regulate hormone synthesis can autonomously secrete excess thyroid hormone, referred to as toxic nodular disease. Toxic nodular disease, the second most common cause of hyperthyroidism, is more common in iodine-deplete regions, with an incidence ranging from 1.5-18 cases/100,000-person/years worldwide.[1,5,6] In early pregnancy, human chorionic gonadotrophin (hCG) stimulates the thyroidal TSH receptor, causing increased thyroid hormone synthesis. Autoimmunity (postpartum or sporadic painless thyroiditis), infection, some medications, and trauma to the thyroid can cause thyroidal inflammation and release of stored hormones into the bloodstream, causing thyrotoxicosis but not hyperthyroidism, as there is no increase in thyroid hormone synthesis (Table 1). Amiodarone causes two types of thyrotoxicosis (AIT). Type 1 AIT results from increased thyroid hormone synthesis due to the high iodine content of amiodarone acting as excess substrate for thyroid hormone production. Type 2 AIT is a destructive thyroiditis leading to release of preformed thyroid hormone from thyroid gland. As treatments differ for the two types of AIT, it is important to distinguish between them. Immune-checkpoint inhibitors are increasingly used for treatment of certain cancers, such as breast cancer, lung cancer, and melanoma. Among these, anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4) antibody and anti-programmed cell death 1 (PD-1) antibody treatment have been associated with multiple immune-related adverse endocrine effects. Thyroid dysfunction is the most common endocrine effect, and both hyperthyroidism and the thyrotoxic phase of thyroiditis have been reported after treatment with these agents.[7]Hyperthyroidism can also be caused by excess exogenous thyroid hormone ingestion. Subclinical hyperthyroidism can result from any of the etiologies that cause overt hyperthyroidism.[8]

Clinical Presentation

Clinical manifestations of thyrotoxicosis include anxiety, insomnia,[9] palpitations,[10] weight loss from increased metabolism and energy expenditure, diarrhea or loose stools, excessive sweating, heat intolerance, and irregular menses.[11] Approximately 2% of older people with hyperthyroidism present with “apathetic” hyperthyroidism with minimal symptoms.[3,12] Patients with Graves’ disease or toxic nodules may report increased neck size or compressive symptoms from the enlarged thyroid gland, such as dysphagia, orthopnea, or voice changes. Thyroid pain and tenderness are present in subacute thyroiditis, which is often preceded by a viral upper respiratory infection. Subclinical hyperthyroidism is usually asymptomatic or causes symptoms similar to but milder than those of overt hyperthyroidism.

COVID-19 and hyperthyroidism—During the SARS-CoV2 (COVID) pandemic, cases of Graves’ disease and subacute thyroiditis related to COVID infection or vaccination were reported, presumably due to the immunogenic nature of COVID.[13,14,15] A retrospective study reported a two-fold increase in the incidence of Graves’ disease in a Spanish hospital in 2020-2021 compared to the pre-COVID period of 2017-2019.[16]

Assessment and Diagnosis

Physical Examination—Physical examination findings may vary depending on circulating thyroid hormone levels, hyperthyroidism duration, and the underlying etiology.

All causes of thyrotoxicosis may cause tachycardia, systolic hypertension, a stare, lid lag (when the upper lid remains elevated on downward gaze due to activation of sympathetic tone), tremor, and proximal muscle weakness. Other signs are specific to disease etiology. Thyroid nodules (autonomous nodules) or a diffusely enlarged thyroid gland, sometimes with a bruit (Graves' disease), may be palpable. The most common extrathyroidal Graves' disease manifestation is orbitopathy, occurring in up to 25% of patients with Graves' disease. This presents as conjunctival erythema, periorbital edema, lid retraction, and proptosis. Other extrathyroidal Graves' disease manifestations include pretibial myxedema (pink or purple indurated papules, sometimes with accompanying lymphedema and elephantiasis on the anterior lower leg), which occurs in about 1.5% of patients with Graves disease, and acropachy (swelling in digits and nail clubbing) which occurs in about 0.3% of patients with Graves disease.[17]

Laboratory Testing—Low serum TSH is the best test to detect thyroid dysfunction, and it has the highest sensitivity (92-95%) and specificity (89-85%) for the diagnosis of thyroid dysfunction.[18] Thyroid hormone may circulate as T3 or as T4, a prohormone which is converted to T3 in peripheral tissues. T3 is the physiologically active form of thyroid hormone. Free T4 levels can be used to assess the degree of hyperthyroidism. T3 levels can also help establish the cause and severity of thyrotoxicosis. The total T3:T4 ratio is generally >20:1 in Graves' disease or toxic nodules, but <20:1 in thyroiditis.[3] Currently available free T3 assays are not accurate and thus total T3 levels may be preferred.[3]

Once thyrotoxicosis is confirmed, the etiology should be ascertained (Figure 1, Table 2). The presence of TSH-receptor antibodies (TRAbs) is pathognomonic for Graves disease.[19] Current guidelines recommend measuring TRAb as the initial step in differentiating Graves' disease from other causes of thyrotoxicosis.[3,20] Two assay types are available for TRAb measurement.[21] TRAb binding immunoassays measure both stimulating and blocking antibodies, while functional bioassays assess activity of thyroid stimulating immunoglobulin (TSI). Current 3rd-generation TRAb assays have a high sensitivity (97.7%) and specificity (99.5%) for the diagnosis of Graves disease.[22] Serum TSI concentrations correlate with the degree of extrathyroidal Graves disease manifestations.[19,21]

Biotin effects on thyroid testing—A false positive diagnosis of hyperthyroidism may occur due to immunoassay interference. Biotin is a soluble vitamin that is commonly used as a supplement for hair and nails. High-dose biotin intake can lead to falsely low serum TSH and high FT4 and T3 levels in immunoassays utilizing biotin-streptavidin interactions.[23] Excess biotin may also cause false positive TRAb results. When the clinical presentation is not consistent with the laboratory findings, a history regarding supplement use should be obtained. If biotin interference is suspected, biotin can be stopped for 2-7 days before repeat testing.

Imaging Studies—Thyroid scintigraphy using radioactive iodine (RAI) or technetium is recommended if palpable thyroid nodules are present or if the thyrotoxicosis etiology is unclear after TRAb testing. Thyroid scintigraphy assesses activity of thyroid gland by measuring uptake of iodine or technetium. RAI uptake is diffusely increased in Graves' disease and focally or heterogeneously increased in toxic adenoma or toxic nodules. RAI

uptake is low or absent in thyroiditis, high iodine exposure, or extrathyroidal sources of thyroid hormone. In pregnancy and lactation when scintigraphy is contraindicated, thyroid ultrasound with color flow Doppler can be used. Gland vascularity is generally increased in Graves' disease, indicating increased gland activity, but low or absent in thyroiditis, in which thyroid gland activity is not increased. A study of tests to diagnose Graves disease found the following sensitivities by test: TRAb: 93%, TSI: 94.2%, thyroid ultrasound demonstrating diffusely increased thyroid vascularity: 92.1%, and thyroid scintigraphy demonstrating diffusely increased thyroid vascularity: 95.3%.[24] However, the specificity of thyroid ultrasound for diagnosis of Graves' disease was only 69.8%.

Thyrotoxicosis Treatment

Untreated overt thyrotoxicosis, especially in older individuals, may cause osteoporosis and atrial fibrillation and, rarely, high-output heart failure,[10] from the effect of excess thyroid hormone on the thyroid hormone receptors present in bone and heart. Atrial fibrillation is present in 10-25% of patients with thyrotoxicosis, with higher risks in men and those aged >65 years.[10] Treatment should be patient-centered and individualized, taking into account age, comorbidities, severity of hyperthyroidism, likelihood of remission, plans for pregnancy, available surgical expertise, and patient preferences.[25] Treatment choices should be informed by understanding the underlying etiology. In patients with Graves disease, treatment should focus on controlling hyperthyroidism with anticipated eventual remission of Graves disease, while causes of hyperthyroidism due to toxic nodular disease require indefinite treatment if antithyroid drugs are used because this does not remit (Figure 2). Symptomatic patients with all forms of thyrotoxicosis may benefit from initiation of beta blockers, which decreases heart rate and improves hyperadrenergic symptoms,[26] but is relatively contraindicated in patients with bronchospastic disease. Beta blockade is typically the only therapy required in thyrotoxicosis due to thyroiditis, as this disorder is self-limited and there is no indication for antithyroid drug therapy in the absence of increased thyroid hormone synthesis.[3] Most patients with overt hyperthyroidism from autonomous thyroid nodules or Graves' disease will require treatment with antithyroid drugs (ATD), radioactive iodine ablation, or surgery. U.S costs, excluding visits and testing, have been estimated as $300-400 for ATDs, $4000-5000 for radioactive iodine, and $30,000-40,000 for surgery.[27] However, assessments of the most cost-effective treatment modality have varied in different settings.[28-30] Practice patterns in the U.S. have shifted to prioritize ATD rather than radioactive iodine treatment as the initial treatment modality, which is more in line with practices in other regions.[31,32]

Antithyroid drugs

Thionamides (methimazole [MMI], carbimazole, which is metabolized to MMI, and propylthiouracil [PTU]) decrease thyroid hormone synthesis and secretion and can restore euthyroidism in patients with hyperthyroidism. MMI is the first-line agent for people who are not within the first trimester of pregnancy. The starting MMI dose for Graves' disease can be based on severity: 5-10 mg/day for FT4 concentrations 1.0-1.5 times the upper limit of normal, 10-20 mg/day for FT4 1.5-2.0 times the upper limit of normal, and 30-40 mg/day for FT4 2-3 times the upper limit of normal.[3] Thyroid function tests should be monitored every 4-8 weeks after treatment initiation, and MMI can often be titrated down

to a maintenance dose of 5-10 mg/day as hyperthyroidism improves. High-dose MMI in combination with levothyroxine (a “block and replace” regimen) is not recommended for routine use in Graves’ disease patients, because the high ATD doses required may increase the likelihood of toxicity and a clear benefit has not been established.[33] In patients with autonomous thyroid nodules , MMI dose requirements are typically ≤10 mg/day, and thyroid function tests should be monitored every 3 months at least initially. In both Graves’ disease and toxic nodular disease, thyroid function tests may need to be monitored every 2-4 months, especially after initiation of ATDs, as dose adjustment is frequently needed.

For patients with Graves’ disease, ATD treatment can be discontinued after 12-18 months if serum TSH has normalized and the TRAb is no longer positive.[3] TRAb titers typically decline over the course of treatment and resolve in 70-80% by 18 months of therapy.[34] Overall, reported remission rates (euthyroidism a year following ATD discontinuation) after an initial 12-18 months of ATD therapy are 30-50%,[35-37] although the likelihood is much lower (0-20%) if TRAb remains positive.[3,38] The likelihood of remission may increase with longer duration of ATD treatment, with remission rates up to 80-85% reported in selected patients after >5 years of treatment.[37,39] Individuals <40 years of age, with higher thyroid hormone levels at baseline, with higher baseline TRAb titers, and with larger goiters are less likely to attain remission.[36,40] Hyperthyroidism recurrence is most likely in the first 6 months following ATD discontinuation, especially if the TRAb level remains elevated. In Graves’ disease, patients who do not achieve remission after 12-18 months, or in those whose hyperthyroidism remits and then recurs, definitive therapy with radioactive iodine or thyroidectomy should be considered.[3] However, MMI has been shown to be safe and effective for as long as 24 years.[41,42] TRAb titers can be assessed every 1-2 years, and thyroid function testing every 4-6 months, in patients on long-term ATD treatment.[3]

Patients should be carefully counseled about potential adverse effects of ATDs before treatment initiation. Overall, adverse effects are reported in approximately 13% of patients.[43] The most frequent adverse effect is pruritis and/or rash (occurring in 6% on MMI and 3% on PTU), which can typically be managed with antihistamines.[3,43] Successful desensitization protocols have been described for patients with MMI allergy.[44] Rare side effects include agranulocytosis, which occurs in 0.2-0.5% of patients and most frequently in the first 90 days after treatment initiation.[45,46] Rare cases of fulminant hepatic failure resulting in death or need for liver transplant have been reported with PTU use.[47] Both ATDs can cause hepatitis, and hepatic injury is reported in approximately 2.7% of patients on PTU and 0.4% on MMI.[43] Risk of liver injury is highest in the first 90 days after ATD initiation.[48] Baseline complete blood count (CBC) and liver function testing (LFT) is recommended prior to initiating ATD treatment, although it is unclear whether there is any benefit of ongoing CBC or LFT monitoring in patients treated with anti-thyroid drugs.[3] Uncontrolled hyperthyroidism is also associated with at least one abnormal liver function test in 55% of patients at baseline, with results normalizing in the majority of patients after initiation of ATD treatment, even when baseline transaminases are five times the upper limit of normal.[49] Antineutrophil cytoplasmic antibody-associated small-vessel vasculitis has been reported in up to 3% of ATD-treated patients, with the risk being three-fold higher with PTU than with MMI and increasing with duration of use.[50] Pancreatitis is newly listed

as an adverse MMI effect in Europe, although data for this are conflicting. The absolute risk over the initial 18 months of therapy appears to be <0.4%.[51,52]

Radioactive iodine treatment—RAI treatment cures hyperthyroidism in more than 90% of patients with Graves' disease or autonomous thyroid nodules.[32,53] Factors associated with persistent hyperthyroidism after RAI treatment in Graves' disease include male sex, prior ATD therapy, treatment >6 months after GD diagnosis, elevated FT4 level, larger thyroid volume, and higher RAI uptake.[54] Beta blockade and pre-treatment MMI are recommended in older patients and those at particularly high risk of cardiovascular events in case of transiently worsening hyperthyroidism following RAI treatment.[3] If employed, MMI should be stopped 2-7 days prior to treatment and may be re-started 3-7 days post-therapy.[3,55] The goal of therapy in Graves' disease is rendering a patient hypothyroid, while in toxic nodular goiter, the goal is merely to alleviate hyperthyroidism. The eventual likelihood of developing hypothyroidism after RAI treatment for autonomous thyroid nodules is dependent on the administered activity but may be up to 60%.[56,57] Following RAI, thyroid function tests should be measured every 4-6 weeks for 6 months, or until the patient has become hypothyroid and is stable on thyroid hormone replacement. If hyperthyroidism persists after 6 months, repeat RAI dosing is recommended.[3]

RAI may cause or exacerbate eye disease in Graves' patients, particularly in people who smoke cigarettes or in those with very high TRAb titers. To prevent this, pretreatment with prednisone 0.3-0.5 mg/kg/day, tapered over 3 months, should be used in people who smoke cigarettes, those with high TRAb levels, or those with preexisting thyroid eye disease.[58] Whether or not RAI treatment for hyperthyroidism is associated with increased long-term risk for future malignancies is unclear, with a recent meta-analysis of 12 studies involving 479,452 people with hyperthyroidism showing no significant association of exposure to RAI therapy with cancer risk, compared to nonexposure (59). However, overall, a linear dose-response association was identified between RAI therapy and mortality due to breast cancer and other solid tumor cancers.[59]

Thyroid Surgery—Thyroidectomy is indicated for patients with hyperthyroidism who have local compressive symptoms from a large goiter, suspicious or malignant thyroid nodules, or moderate to severe Graves ophthalmopathy. Thyroidectomy should be the first-line treatment if concurrent thyroid malignancy is confirmed or suspected.[3] In patients with Graves disease, total thyroidectomy is associated with a lower risk for recurrent hyperthyroidism than subtotal thyroidectomy and is the preferred operation.[3,60] In individuals with toxic adenoma, thyroid lobectomy may be preferred over RAI when rapid resolution is preferred, for cosmesis, or if there are local compressive symptoms from a large thyroid gland.[61] Total thyroidectomy rapidly cures hyperthyroidism from Graves disease or toxic multinodular goiter but results in a lifelong need for thyroid hormone replacement. Potential surgical complications include damage to the recurrent laryngeal nerves, hematoma, and hypoparathyroidism,[62] with higher complication rates for surgeons who have performed relatively few procedures, compared to more experienced surgeons (6.4% vs. 4.1%; P <0.0001).[63] Pre-treatment with ATD lowers risk for thyroid storm at the time of surgery.[61] Preoperative treatment with high-dose iodine (such as saturated solution

of potassium iodide [SSKI] or Lugol's solution) of Graves' disease patients decreases thyroid vascularity and thus operative blood loss, although it may not change risks of postoperative complications.[64] Calcium and/or vitamin D supplementation pre-operatively may decrease risk for postoperative hypocalcemia.[65]

Novel treatments—In selected centers, radiofrequency ablation, which induces necrosis of thyroid tissue using heat energy, is a minimally invasive alternative to surgery or radioactive iodine for the treatment of toxic nodules. This procedure reduces nodule volume by 52%-86% and normalizes thyroid function in 61.7% (95% CI: 48.7%-74.7%).[66] Guidelines recommend restricting this technique to younger patients with small nodules, although it may be considered in those with larger toxic multinodular goiters who are not candidates for surgery or RAI treatment.[67] Novel Graves' disease therapies are currently under investigation, including small molecules, biologies, and immunomodulatory peptides with specific effects at the TSH receptor.[68]

Subclinical Hyperthyroidism

Subclinical hyperthyroidism may resolve spontaneously and progresses to overt hyperthyroidism in approximately 8% of patients at 1 year, and 26% by 5 year follow-up..[69] Progression to overt hyperthyroidism is more common in people with undetectable serum TSH at baseline and in those with toxic multinodular goiter.[69,70] Black Americans have lower mean TSH levels compared to White Americans and a slightly low serum TSH level may be normal in Black Americans, compared to White Americans.[3] Still, subclinical hyperthyroidism is associated with increased risks of atrial fibrillationheart failure, total mortality, cardiovascular mortality, and coronary heart disease events.[71,72] Cardiovascular mortality and atrial fibrillation risks are increased when the serum TSH is <0.1 mlU/L compared to 0.1-0.44 mIU/L.[70] Thyroid hormone enhances both osteoblast and osteoclast action, and excess thyroid hormone leads to increased bone resorption.[73] Serum TSH ≤0.1mIu/L has been associated with 3-4-fold increased hip and spinal fracture risks, especially in postmenopausal women (Absolute rates not provided).[74] Subclinical hyperthyroidism has been associated with a 36% increased hip fracture risk, 28% increased risk of any fracture, and 16% increased non-spine fracture risk compared to euthyroidism, as well as low bone density in both men and women.[75] No placebo-controlled randomized clinical trials have assessed the effects of treatment for subclinical hyperthyroidism. In small and uncontrolled studies, treatment with ATD[76] and RAI[77] has been reported to improve stability of bone density in postmenopausal women. A randomized clinical trial comparing the effects of RAI therapy to 60 months' treatment with ATD in 83 adults with subclinical hyperthyroidism age ≥65 years with baseline serum TSH <0.1 mlU/L found that by the end of the study, 66% of the RAI-treated patients were hypothyroid and 34% remained euthyroid, while 6% ATD-treated patients spontaneously developed hypothyroidism and the other 94% remained euthyroid.[78] Results of bone density and echocardiography were not different between the treatment groups, there were no treatment-associated significant adverse events, and there was no significant difference in treatment costs.

The U.S. Preventive Services Task Force currently recommends against testing or treatment for subclinical hyperthyroidism.[79] However, other U.S. and European guidelines recommend

treatment for subclinical hyperthyroidism when identified in patients over 65 years of age (or in those ≤65 years old with symptoms, osteoporosis, or heart disease) when the serum TSH is consistently <0.1 mIU/L.[3,80] Therapy can be considered in those groups when the TSH is persistently in the 0.1-0.4 mIU/L range, but it should be avoided in asymptomatic patients age <65 in the absence of osteoporosis or heart disease. It is also important to consider the possibility of exogenous subclinical hyperthyroidism from excess T4 repletion for hypothyroidism or thyrotoxicosis factitia.

Pregnancy and lactation

Gestational transient thyrotoxicosis, in which thyroid hormone production increases because of thyroid stimulation by elevated hCG levels, affects approximately 2-11% of pregnancies and is associated with hyperemesis gravidarum.[81] This condition does not require ATD treatment and it is not associated with adverse obstetric outcomes[82]; it can simply be monitored with serial thyroid function testing and it resolves spontaneously as maternal hCG levels decline.[83,84] All other forms of overt hyperthyroidism in pregnancy require treatment to reduce risks for outcomes including preeclampsia, low birth weight, miscarriage, and preterm delivery.[85] Both ATDs are teratogenic, but congenital anomalies are milder and risk lower for PTU than for MMI. PTU-associated anomalies include facial or neck cysts and urinary tract abnormalities, while those associated with MMI include aplasia cutis, esophageal atresia, abdominal wall defects, and ventricular septal defects. In a meta-analysis of 16 cohorts that included 5,367,601 people, the adjusted relative risk for MMI compared to controls was 1.28 (95% CI 1.06-1.54) and that for PTU was 1.16 (95% CI 1.08-1.25) [AU- please provide absolute rates- or say “absolute rates not provided” if that is correct].[86] Therefore, PTU is preferred in the first trimester of pregnancy.[83,84] Because ATDs cross the placenta and have more pronounced effects on fetal than on maternal thyroid function, the lowest ATD dose necessary should be used to maintain the maternal FT4 level at or just above the upper reference limit.[84] ATDs are secreted in breast milk at low levels, but doses up to 20 mg/d of MMI and 450 mg/day of PTU are considered safe in lactation and do not require thyroid function monitoring of the breastfed infant.[83] RAI treatment is contraindicated in pregnancy and lactation.[84] It should be deferred until a minimum of 3 months after breastfeeding is completed, to allow for lactation- induced mammary tissue changes to resolve, avoiding radiation exposure which could damage breast tissue.[84,87] If needed, thyroidectomy in pregnancy is safest in the second trimester.[61]

Thyroid Storm

Thyroid storm consists of severe uncontrolled hyperthyroidism and is characterized by multi-organ system failure and a mortality rate of 3.6-17%.[88,89] Presenting symptoms may include fever, tachycardia, heart failure, atrial fibrillation, and various central nervous system abnormalities. Thyroid storm may be precipitated by surgery, amiodarone use, or discontinuation of antithyroid drugs.[89,90] Diagnostic criteria have been published by Burch and Wartofsky[91] and by the Japanese Thyroid Association.[92] Management is aimed at rapidly reducing circulating T3 levels using antithyroid drugs, glucocorticoids, beta blockade, inorganic iodide, and cholestyramine.[3] Although both ATDs decrease thyroid hormone synthesis, U.S. guidelines recommend PTU for patients with thyroid storm

since PTU, but not MMI, blocks T4 to T3 conversion.[3] However, a recent comparative effectiveness study found no difference in in-hospital mortality, costs, adverse events, or duration of organ support in those treated with PTU compared to MMI.[93] In addition to lowering serum T3 levels, patients should be treated in the intensive care unit and any precipitating illness should be addressed.[3] Plasmapheresis to lower circulating T3 levels may be considered in refractory[94]

Prognosis

Compared to euthyroidism, overt hyperthyroidism is associated with a 35-400% increase in all-cause mortality, varying according to the acuity and severity of hyperthyroidism, and a 20% increase in cardiovascular mortality .[95,96] The exact mechanism is not clear, but increased mortality risks of hyperthyroidism are thought to be related to increased risks of endothelial damage and hypercoagulability. Mortality is associated with the cumulative duration of time spent hyperthyroid, regardless of the treatment modality employed.[97,98] A network meta-analysis that included three retrospective Graves' disease cohorts concluded that while all three major treatment modalities were associated with lower risks for congestive heart failure and arrhythmia, surgery was associated with greater benefit than ATD or RAI.[99] Similarly, a registry study of 10,992 people that compared mortality after treatment for hyperthyroidism concluded that all-cause mortality was lower following surgery than after RAI treatment (absolute rates not provided). [100] A registry-based study reported that all-cause and cardiovascular mortality risk may be higher among patients treated for toxic multinodular goiter compared to those treated for Graves' disease.[101]

Limitations

This review has several limitations. First, some relevant papers may have been missed. Second, a formal literature quality assessment was not performed. Third, management of nonthyroidal aspects of Graves' disease, such as orbitopathy and dermatopathy, was not covered.

Conclusion

Hyperthyroidism affects 2.5% of adults worldwide and is associated with osteoporosis, heart disease, and increased mortality. First-line treatments are antithyroid drugs, thyroid surgery, and RAI treatment. Treatment choices should be individualized and patient-centered.

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Frequently Asked Questions

1. How should asymptomatic patients with subclinical hyperthyroidism be managed?

Abnormal thyroid function test results should be confirmed with repeat labs in 2-3 months. If serum TSH remains persistently low with normal free thyroxine (T4) and total triiodothyronine (T3) levels, TRAb testing and possibly thyroid scintigraphy may be used to determine the underlying etiology. Treatment with antithyroid drugs is recommended in patients over 65 years of age (or in those ≤65 years old with symptoms, osteoporosis, or heart disease) when the serum TSH is consistently <0.1 mlU/L.

2. What is the first-line treatment for Graves' disease?

Most symptomatic patients with Graves' disease can be started on antithyroid drugs to decrease synthesis and release of excess thyroid hormone. A beta-blocker can be used initially to control tachycardia and palpitations in symptomatic patients, and can be discontinued once thyroid hormone levels improve. Definitive treatment options including thyroidectomy and radioactive iodine ablation can be considered once hyperthyroidism is reasonably controlled.

3. How should a patient with a nodular goiter on exam and a persistently low serum TSH level be evaluated?

The most likely causes of hyperthyroidism in this setting include Graves' disease and autonomously functioning nodule (toxic multinodular goiter or toxic adenoma). Thyroid ultrasound can confirm the presence of nodules and to assess risks for thyroid malignancy. Thyroid scintigraphy should next be performed to determine the etiology of the hyperthyroidism. This helps distinguish between hyperfunctioning nodules (which do not require biopsy) and hypofunctioning nodules (which may require biopsy, depending on size and ultrasonographic characteristics).

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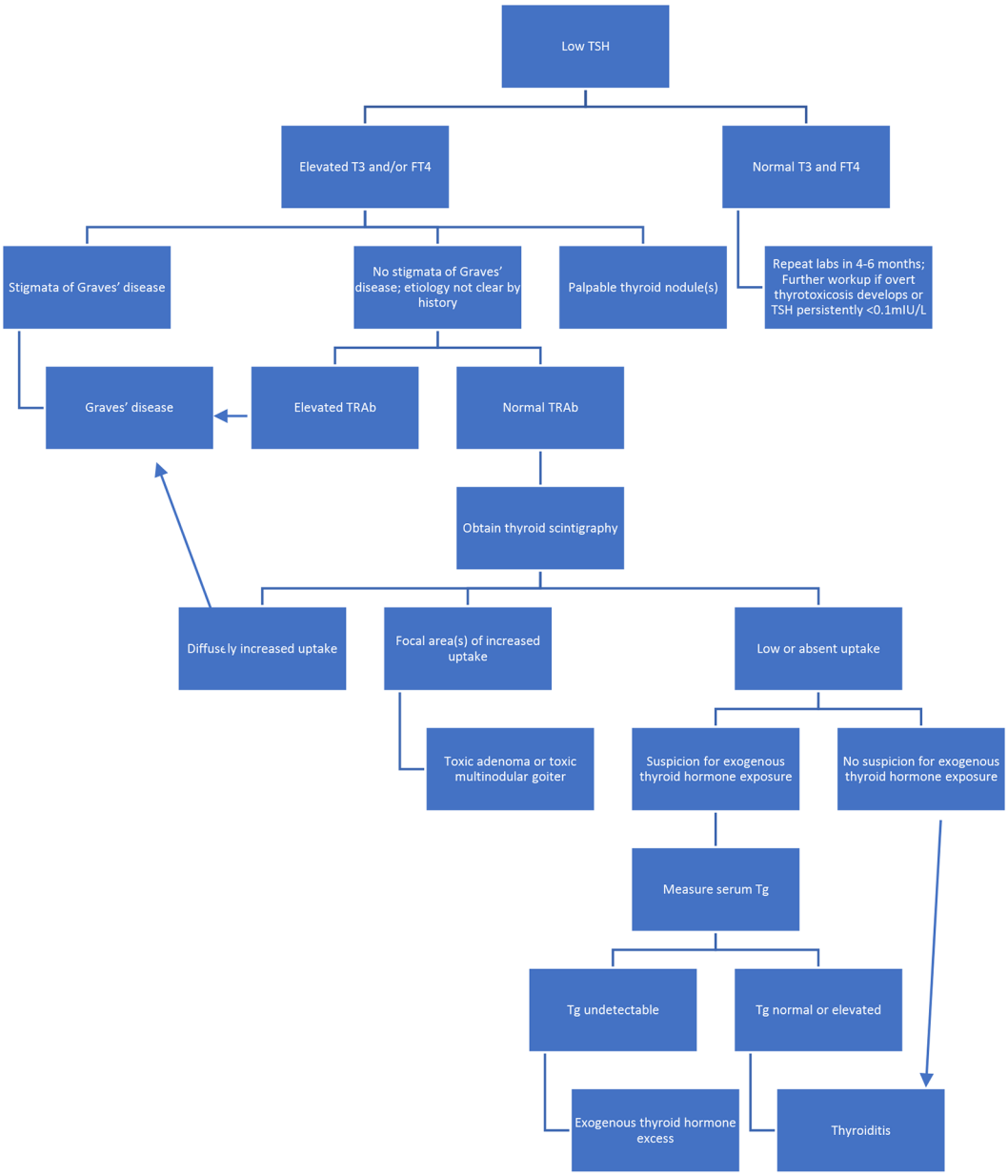

Figure 1.

Assessment of Thyrotoxicosis

TSH = thyroid stimulating hormone; T3 = triiodothyronine; T4 = thyroxine; TRAb = TSH-receptor antibody; Tg = thyroglobulin.

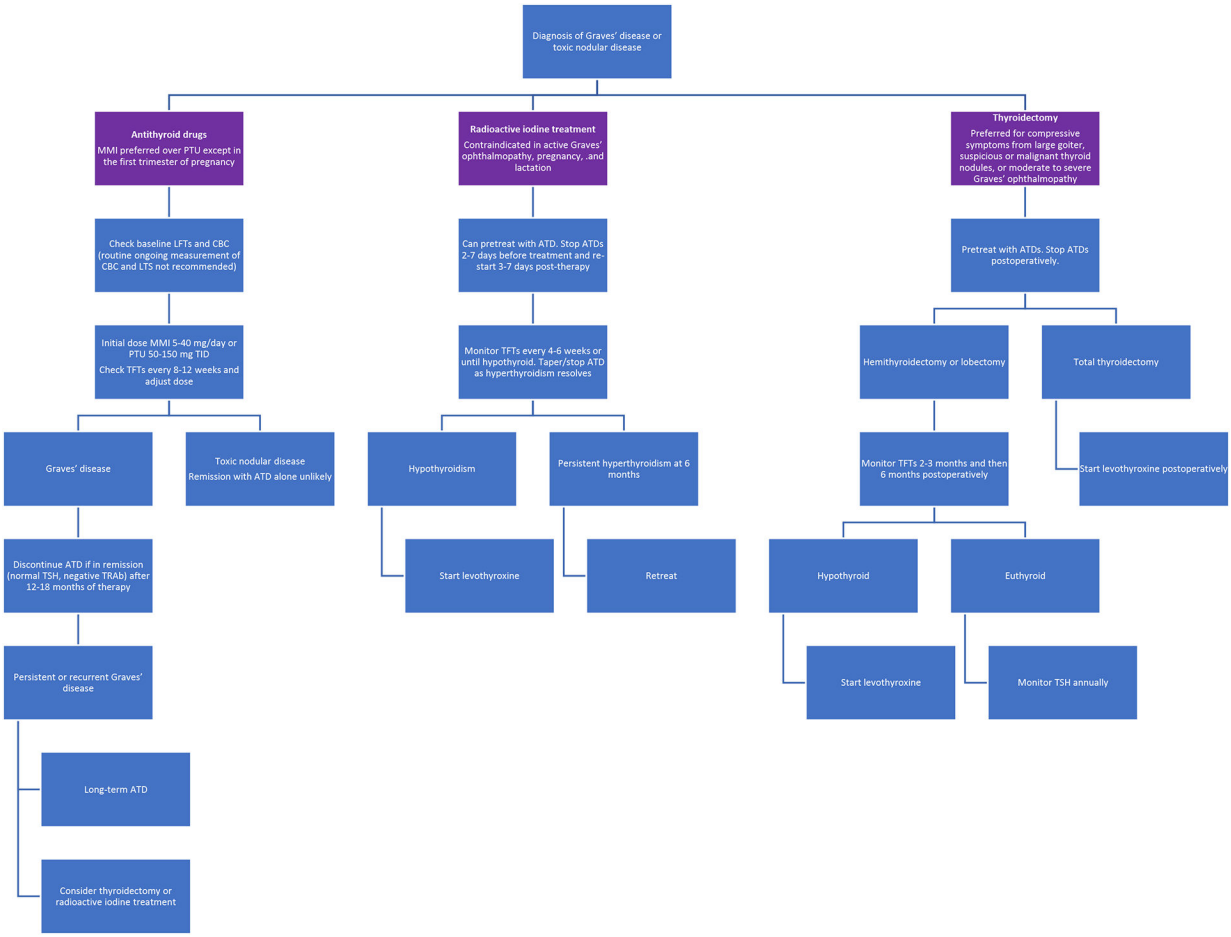

Figure 2.

Treatment of Hyperthyroidism

TSH = thyroid stimulating hormone; MMI = methimazole; PTU = propylthiouracil; LFTs = liver function tests; CBC = complete blood count; ATD = antithyroid drug; TRAb = antibody to TSH receptor; TFTs = thyroid function tests.

Table 1.

Epidemiology of different causes of thyrotoxicosis- Can we have separate columns for prevalence and incidence so that we don't confuse readers

Etiology	Prevalence	Incidence	Pathophysiology
Graves' disease[102,103]	2% in women, 0.5% in men globally	20-40 cases per 100,000 people per year	Stimulation of thyroid gland by TRAb, leading to increased synthesis and release of thyroid hormone
Toxic multinodular goiter[1,5]	-	1.5-18 cases/100,000-person/year	Monoclonal expansion of follicular cells leading to increased production of thyroid hormone from thyroid nodules
Solitary toxic nodules[1]	-	1.6-3.6 cases/100,000-person/year	Germline or somatic activating gene variant leading to autonomous secretion of excess thyroid hormone from a single thyroid nodule
Thyroiditis	8% of postpartum women[104]	0.49-4.9 cases/100,000-person/year	Thyroidal inflammation and release of preformed thyroid hormone from the thyroid gland
Amiodarone-induced thyrotoxicosis (AIT)[105]	11.6% in patients treated with amiodarone	-	• Type 1 AIT: increased production of thyroid hormone from exposure to high iodine content in amiodarone • Type 2 AIT: thyroidal inflammation and release of preformed thyroid hormone from the thyroid gland
Immune checkpoint inhibitor-induced thyrotoxicosis (including both hyperthyroidism and the thyrotoxic phase of thyroiditis)	23-31% overt and subclinical thyrotoxicosis in patients treated with medication[7] Usually occurs within 1-2 months, but can occur up to 6-12 months after initiating therapy	2.9% overall incidence (1.7% with anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4) antibody treatment; 3.2% with anti-programmed cell death 1 (PD-1) antibody treatment; 8.0% during combined anti-PD-1 and anti-CTLA-4 antibody treatment)[106]	Triggering an autoimmune response to the thyroid gland leads to inflammatory thyroiditis

Abbreviations: TRAb, TSH receptor antibody; CTLA-4, anti-cytotoxic T-lymphocyte antigen 4; PD-1, anti-programmed cell death 1.

Table 2.

Diagnosis by type of thyrotoxicosis

Etiology	Description	Signs and Symptoms	Testing
Hyperthyroidism			
Graves' disease	Increased thyroid hormone production and release due to stimulation by TSH receptor antibody (TRAb)	Physical exam findings may include diffusely enlarged thyroid gland with a bruit, and presence of extrathyroidal manifestations of Graves' disease (orbitopathy, pretibial myxedema, acropachy)	• TRAb or TSI positivity (sensitivity 97.7%, specificity 99.5%)[22] • Diffuse uptake on thyroid scintigraphy; increased radioactive iodine uptake (sensitivity 95.3%, specificity 96.4%)[24]
Gestational transient thyrotoxicosis	Increased thyroid hormone production due to stimulation by high levels of hCG	• Often associated with hyperemesis gravidarum • Always in early gestation	• TRAb or TSI is absent • Usually associated with high serum hCG levels
TSH-producing pituitary adenoma	Pituitary adenoma with autonomous secretion of TSH	• Typical symptoms of hyperthyroidism • May have visual field deficit if pituitary macroadenoma is present	• Normal or elevated TSH with elevated T4 and T3 • Pituitary adenoma on MRI
• Toxic adenoma • Toxic multinodular goiter	Autonomous production of excess thyroid hormone from thyroid nodule(s)	Palpable thyroid nodules on exam	"Hot" nodules on thyroid scintigraphy, characterized by increased uptake in the hyperfunctioning nodule(s) with relatively suppressed uptake in the remainder of the thyroid gland
• Type 1 Amiodarone-induced thyrotoxicosis • Excess iodine exposure (i.e., iodinated IV contrast for CT scan)	Increased thyroid hormone production from excess iodine availability	May have toxic nodular disease or previously occult Graves' disease[3]	Low Radioiodine uptake on thyroid scintigraphy
Thyrotoxicosis without hyperthyroidism			
• Painless thyroiditis • Postpartum thyroiditis • Subacute (painful) thyroiditis • Drug-induced thyroiditis • Type 2 Amiodarone-induced thyrotoxicosis • Suppurative thyroiditis	Thyroidal inflammation leading to release of preformed thyroid hormone from the thyroid gland	• History of inciting event or medications such as amiodarone, lithium, interference-α, immune checkpoint inhibitor • Subacute thyroiditis: presence of neck tenderness and elevated ESR	• Low or absent radioiodine uptake on thyroid scintigraphy • Ratio of total T3:T4 <20, reflecting ratio of stored hormones in the thyroid gland
• Thyrotoxicosis factitia • Iatrogenic thyrotoxicosis from excess T4 repletion	Excess availability of exogenous thyroid hormone	Symptoms of thyrotoxicosis	• Low uptake on thyroid scintigraphy • Low or undetectable serum Tg levels

Abbreviations: TRAb, TSH-receptor antibody; TSI, thyroid stimulating immunoglobulin; TSH, thyroid stimulating hormone; hCG, human chorionic gonadotrophin; Tg, thyroglobulin; T4, thyroxine; T3, triiodothyronine; ESR, erythrocyte sedimentation rate; MRI, magnetic resonance imaging.

Table 3.

Treatment for hyperthyroidism due to Grave Disease and autonomous functioning nodules

Treatment category	Mechanism of action	Efficacy	Adverse effects	Patient factors favoring choice	Patient factors against choice
Antithyroid drugs: methimazole (MMI), carbimazole (CMZ), prophylthiouracil (PTU)	Decrease thyroid hormone synthesis	Short-term (≤ 12 months) resolution of hyperthyroidism in nearly all patients, but long-term remission in only 30-50% of those with Graves' disease[32,35]	• Rash in 6% on MMI and 3% on PTU[43] • Agranulocytosis in 0.2-0.5%[43] • Hepatotoxicity in 2.7% of patients on PTU and 0.4% on MMI (rare cases of fulminant hepatic failure with PTU)[43] • Teratogenicity (17.8 per 1000 for MMI and 10.2 per 1000 for PTU)[107] • Possible pancreatitis risk with MMI (<0.4%)[52] • ANCA vasculitis (<1% MMI and 3% PTU)[50]	• Desire to avoid permanent hypothyroidism. • Current pregnancy • Graves' disease with high probability of remission: mild hyperthyroidism, small goiter, and low-titer TRAb. • Moderate-severe TED.	Lifelong treatment needed in patients with autonomous thyroid nodules. Greatest risk of relapse in Graves' disease.
Radioactive iodine	Thyroid tissue destruction	93%[32]	• Cause or exacerbate Graves' eye disease in 6%[32] • Possible long-term increased risk for breast cancer and other solid tumors. • Permanent hypothyroidism in nearly all patients after treatment for Graves' disease and in 30-60% after treatment for autonomous thyroid nodules[56,57]	• Intolerance of ATDs. • Preference to avoid surgical scar or need for general anesthesia for treatment of autonomous thyroid nodules.	• Current pregnancy or lactation or pregnancy planned within 6 months. • Moderate to severe TED or smoker
Thyroidectomy: total or subtotal	Remove thyroid tissue	99% for total thyroidectomy[32]	• Recurrent laryngeal nerve injury or hypoparathyroidism in 4-6%[63]. • Permanent hypothyroidism in 100% after total thyroidectomy and 14% after lobectomy for autonomous nodule[108]	• Moderate-severe TED. Compressive symptoms from goiter. • Known or concern for thyroid malignancy.	• Prefers to avoid lifelong need for thyroid hormone replacement after total thyroidectomy. • Concern about scar. • Lack of access to experienced thyroid surgeon. • Comorbiditi es increasing surgical risk.
Radiofrequency ablation	Thyroid tissue destruction	Normalization of thyroid function in 61.7% with autonomous thyroid nodules (95% CI 48.7%-74.7%)[66]	• Overall complication rates 2.4-3.3% (voice change, nodule rupture, skin bums, brachial plexus injury)[66]	Preference to avoid surgical scar or need for general anesthesia for treatment of toxic adenoma.	• Not appropriate for treatment of Graves' disease. • Ineffective for large multinodular goiter. • Lack of access outside select centers.

Abbreviations: ANCA, Antineutrophilic cytoplasmic antibody; MMI, methimazole or carbimazole; CMZ, carbimazole; PTU, propylthiouracil; TED, thyroid eye disease.