JAMA | Review

Hyperthyroidism
A Review

Sun Y. Lee, MD, MSc; Elizabeth N. Pearce, MD, MSc

IMPORTANCE Overt hyperthyroidism, defined as *suppressed thyrotropin* (previously thyroid-stimulating hormone) and high concentration of triiodothyronine (T_3) and/or free thyroxine (FT_4), affects approximately 0.2% to 1.4% of people worldwide. Subclinical hyperthyroidism, defined as low concentrations of thyrotropin and normal concentrations of T_3 and FT_4, affects approximately 0.7% to 1.4% of people worldwide. Untreated hyperthyroidism can cause cardiac arrhythmias, heart failure, osteoporosis, and adverse pregnancy outcomes. It may lead 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 a diffusely enlarged thyroid gland, stare, or exophthalmos on examination. Patients with toxic nodules (ie, in which thyroid nodules develop autonomous function) 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 thyrotropin-receptor antibody status. Thyroid scintigraphy is recommended if thyroid nodules are present or the etiology is unclear. Thyrotoxicosis from thyroiditis may be observed if symptomatic or treated with supportive care. Treatment options for overt hyperthyroidism from autonomous thyroid nodules or Graves disease include antithyroid drugs, radioactive iodine ablation, and surgery. Treatment for subclinical hyperthyroidism is recommended for patients at highest risk of osteoporosis and cardiovascular disease, such as those older than 65 years or with persistent serum thyrotropin level less than 0.1 mIU/L.

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 radioactive iodine treatment. Treatment choices should be individualized and patient centered.

JAMA. 2023;330(15):1472-1483. doi:10.1001/jama.2023.19052

Multimedia

CME at jamacmelookup.com

Author Affiliations: Section of Endocrinology, Diabetes, Nutrition, and Weight Management, Boston University Chobanian and Avedisian School of Medicine, Boston, Massachusetts.

Corresponding Author: Elizabeth N. Pearce, MD, MSc, Section of Endocrinology, Diabetes, Nutrition, and Weight Management, Boston University Chobanian and Avedisian School of Medicine, 72 E Concord St, C3, Boston, MA 02118 (elizabeth.pearce@bmc.org).

Section Editor: Mary McGrae McDermott, MD, Deputy Editor.

The global prevalence of hyperthyroidism in iodine-sufficient countries is estimated at 0.2% to 2.5%.[1] The prevalence of overt hyperthyroidism, defined as low thyrotropin (previously thyroid stimulating hormone) levels with elevated triiodothyronine (T_3) and/or free thyroxine (FT_4), is approximately 0.2% to 1.4%. The prevalence of subclinical hyperthyroidism, defined as low thyrotropin levels with normal peripheral thyroid hormone levels, is approximately 0.7% to 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 increases in extrathyroidal thyroid hormone availability due to excess levothyroxine repletion, surreptitious thyroid hormone ingestion, or struma ovarii, a type of ovarian dermoid tumor 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 (**Box**).

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, meta-analyses, systematic reviews, and observational studies. Current practice guidelines were also reviewed for content and additional references. We manually searched the references of selected articles, reviews, meta-analyses, and guidelines. A total of 2185 articles were retrieved from the initial search. Of these, 108 were included for this review (4 randomized clinical trials, 21 systematic reviews 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 thyrotropin 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**).[1,4-11] 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 to 18 cases per 100 000 person-years worldwide.[1,6,12] In early pregnancy, human chorionic gonadotrophin (hCG) stimulates the thyroidal thyrotropin 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 the release of stored hormones into the bloodstream, causing thyrotoxicosis but not hyperthyroidism because there is no increase in thyroid hormone synthesis (Table 1). Amiodarone causes 2 types of thyrotoxicosis. Type 1 results from increased thyroid hormone synthesis due to the high iodine content of amiodarone acting as excess substrate for thyroid hormone production. Type 2 is a destructive thyroiditis leading to release of preformed thyroid hormone from the thyroid gland. Because treatments differ for the 2 types of thyrotoxicosis, 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, anticytotoxic 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.[10] Hyperthyroidism can also be caused by excess exogenous thyroid hormone ingestion. Subclinical hyperthyroidism can result from any of the etiologies that cause overt hyperthyroidism.[13]

Clinical Presentation

Clinical manifestations of thyrotoxicosis include anxiety, insomnia,[14] palpitations,[15] weight loss from increased metabolism and energy expenditure, diarrhea or loose stools, excessive sweating, heat intolerance, and irregular menses.[16] Approximately 2% of older people with hyperthyroidism present with apathetic hyperthyroidism with minimal symptoms.[3,17] 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.

Box. Frequently Asked Questions

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

Abnormal thyroid function test results should be confirmed with repeat blood tests in 2 to 3 months. If serum thyrotropin (previously thyroid-stimulating hormone) levels remain persistently low with normal free thyroxine (FT_4) and total triiodothyronine (T_3) levels, thyrotropin receptor antibody (TRAb) testing and possibly thyroid scintigraphy may be used to determine the underlying etiology. Treatment with antithyroid drugs is recommended for patients older than 65 years or for those 65 years or younger with symptoms, osteoporosis, or heart disease when the serum thyrotropin level is consistently less than 0.1 mIU/L.

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

Most symptomatic patients with Graves disease can start taking antithyroid drugs to decrease synthesis and secretion of excess thyroid hormone. A β-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 examination and a persistently low-serum thyrotropin 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 assess risks of thyroid malignancy. Thyroid scintigraphy should next be performed to determine the etiology of the hyperthyroidism. This helps to distinguish between hyperfunctioning nodules, which do not require biopsy, and hypofunctioning nodules, which may require biopsy, depending on size and ultrasonographic characteristics.

COVID-19 and Hyperthyroidism

During the SARS-CoV-2 (COVID-19) pandemic, cases of Graves disease and subacute thyroiditis related to COVID-19 infection or vaccination were reported, presumably due to the immunogenic nature of COVID-19.[18-20] A retrospective study reported a 2-fold increase in the incidence of Graves disease in a Spanish hospital in 2020-2021 compared with the pre–COVID-19 years (2017-2019).[21]

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),

Table 1. Epidemiology of Different Causes of Thyrotoxicosis

Etiology	Prevalence	Incidence	Pathophysiology
Graves disease[4,5]	2% in women, 0.5% in men globally	20-40 Cases per 100 000 person-years	Stimulation of thyroid gland by TRAb, leading to increased synthesis and release of thyroid hormone
Toxic multinodular goiter[1,6]		1.5-18 Cases per 100 000 person-years	Monoclonal expansion of follicular cells leading to increased production of thyroid hormone from thyroid nodules
Solitary toxic nodules[1]		1.6-3.6 Cases per 100 000-person-years	Germline or somatic-activating gene variant leading to autonomous secretion of excess thyroid hormone from a single thyroid nodule
Thyroiditis	8% of postpartum women[7]	0.49-4.9 Cases per 100 000-person-years	Thyroidal inflammation and release of preformed thyroid hormone from the thyroid gland
Amiodarone-induced thyrotoxicosis[8]	11.6% in patients treated with amiodarone		• Type 1: Increased production of thyroid hormone from exposure to high iodine content in amiodarone • Type 2: 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)[9]	• 23%-31% Overt and subclinical thyrotoxicosis in patients treated with medication[10] • Usually occurs within 1-2 mo, but can occur up to 6-12 mo after initiating therapy	2.9% Overall incidence (1.7% with CTLA-4 antibody treatment; 3.2% PD-1 antibody treatment; 8.0% during combined PD-1 and CTLA-4 antibody treatment)	Triggering an autoimmune response to the thyroid gland leads to inflammatory thyroiditis

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

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. 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, and acropachy (swelling in digits and nail clubbing), which occurs in about 0.3% of patients.[22]

Laboratory Testing

A low-serum thyrotropin level 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.[23] Thyroid hormone may circulate as T_3 or as T_4, a prohormone, which is converted to T_3 in peripheral tissues. T_3 is the physiologically active form of thyroid hormone. Free T_4 levels can be used to assess the degree of hyperthyroidism. T_3 levels can also help establish the cause and severity of thyrotoxicosis. The total T_3:T_4 ratio is generally more than 20:1 in Graves disease or toxic nodules, but less than 20:1 in thyroiditis.[3] Currently available free T_3 assays are not accurate and thus total T_3 levels may be preferred when the assay option is available.[3]

Once thyrotoxicosis is confirmed, the etiology should be ascertained (**Figure 1**, **Table 2**). The presence of thyrotropin-receptor antibodies (TRAbs) is pathognomonic for Graves disease.[25] Current guidelines recommend measuring TRAb levels as the initial step in differentiating Graves disease from other causes of thyrotoxicosis.[3,24] Two assay types[26] are available: TRAb-binding immunoassays measure both stimulating and blocking antibodies, whereas functional bioassays assess activity of thyroid-stimulating immunoglobulin. Current third-generation TRAb assays have a high sensitivity (97.7%) and specificity (99.5%) for the diagnosis of Graves disease.[27] Serum thyroid-stimulating immunoglobulin concentrations correlate with the degree of extrathyroidal Graves disease manifestations.[25,26]

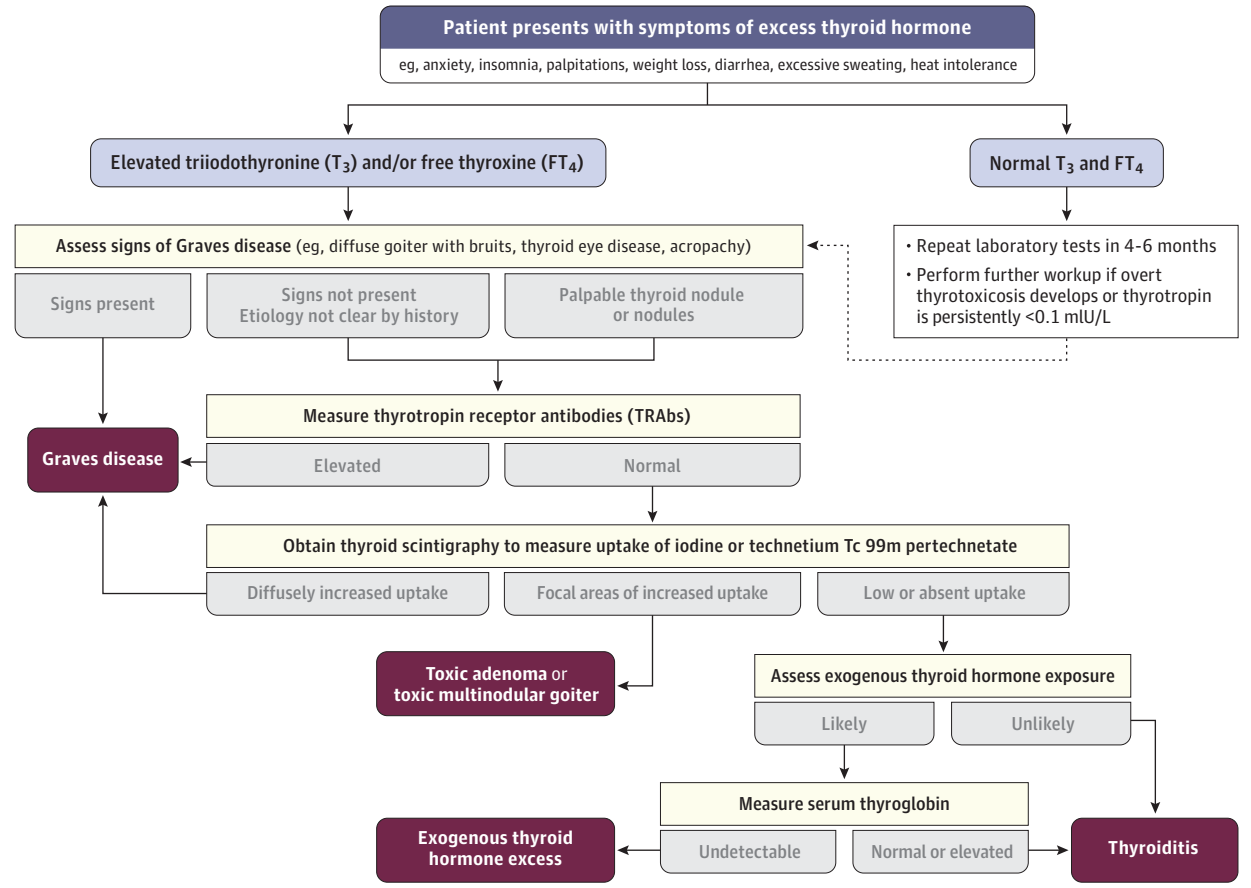
Biotin Effects on Thyroid Testing

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 (> 100 mg/d) intake can lead to falsely low-serum thyrotropin and high FT_4 and T_3 levels in immunoassays using biotin-streptavidin interactions.[28] 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 to 7 days before repeat testing.

Imaging Studies

Thyroid scintigraphy using radioactive iodine or technetium Tc 99m pertechnetate is recommended if palpable thyroid nodules are present or if the thyrotoxicosis etiology is unclear after TRAb testing. Thyroid scintigraphy assesses activity of the thyroid gland by

Figure 1. Assessment of Thyrotoxicosis



measuring uptake of iodine or technetium Tc 99m pertechnetate. Radioactive iodine uptake is diffusely increased in Graves disease and focally or heterogeneously increased in toxic adenoma or toxic nodules. Radioactive iodine uptake is low or absent in thyroiditis, high iodine exposure, or extrathyroidal sources of the 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%; thyroid stimulating immunoglobulin, 94.2%; thyroid ultrasound demonstrating diffusely increased thyroid vascularity, 92.1%; and thyroid scintigraphy demonstrating diffusely increased thyroid vascularity, 95.3%.[29] However, the specificity of thyroid ultrasound for diagnosis of Graves disease was only 69.8%.

Treatment

Untreated overt thyrotoxicosis, especially in older individuals, may cause osteoporosis, atrial fibrillation, and, rarely, high-output heart failure[15] from the effect of excess thyroid hormone on the thyroid hormone receptors present in the bone and heart. Atrial fibrillation is present in 10% to 25% of patients with thyrotoxicosis, with higher risks in men and those older than 65 years.[15] 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 (**Table 3**).[30-41] Treatment choices should be informed by the underlying etiology. In patients with Graves disease, treatment should focus on controlling hyperthyroidism with anticipated eventual remission of Graves disease, whereas 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 β-blockers, which decreases heart rate and improves hyperadrenergic symptoms[42] but is relatively contraindicated for patients with bronchospastic disease. β-Blockade is typically the only therapy required for treating thyrotoxicosis due to thyroiditis because 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, radioactive iodine ablation, or surgery. US costs for a 12- to 18-month treatment course, excluding visits and testing, have been estimated as $300 to $400 for antithyroid drugs, $4000 to $5000 for radioactive iodine, and $30 000 to $40 000 for thyroidectomy.[43] However, assessments of the most cost-effective treatment modality have varied in different settings.[44-46] Practice patterns in the US have shifted to prioritize antithyroid drugs rather than radioactive iodine treatment as the initial treatment modality, which is more consistent with practices in other regions.[30,47]

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 TRAb	Physical examination 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%)[23] • 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
Thyrotropin-producing pituitary adenoma	Pituitary adenoma with autonomous secretion of thyrotropin	• Typical symptoms of hyperthyroidism • May have visual field deficit if pituitary macroadenoma is present	• Normal or elevated thyrotropin with elevated T_4 and T_3 • Pituitary adenoma on MRI
• Toxic adenoma • Toxic multinodular goiter	Autonomous production of excess thyroid hormone from thyroid nodule(s)	Palpable thyroid nodules on examination	"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 (ie, 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, interferon alfa, immune checkpoint inhibitor • Subacute thyroiditis: presence of neck tenderness and elevated ESR	• Low or absent radioiodine uptake on thyroid scintigraphy • Ratio of total T_3:T_4 < 20, reflecting ratio of stored hormones in the thyroid gland
• Thyrotoxicosis factitia • Iatrogenic thyrotoxicosis from excess T_4 repletion	Excess availability of exogenous thyroid hormone	Symptoms of thyrotoxicosis	• Low uptake on thyroid scintigraphy • Low or undetectable serum Tg level

Abbreviations: CT, computed tomography; ESR, erythrocyte sedimentation rate; hCG, human chorionic gonadotrophin; IV, intravenous; MRI, magnetic resonance imaging; T_3, triiodothyronine; T_4, thyroxine; Tg, thyroglobulin; TRAb, thyrotropin receptor antibody; TSI, thyroid-stimulating immunoglobulin.

Antithyroid Drugs

Thionamides (methimazole; carbimazole, which is metabolized to methimazole; and propylthiouracil) decrease thyroid hormone synthesis and secretion and can restore euthyroidism in patients with hyperthyroidism. Methimazole is the first-line agent for people who are not within the first trimester of pregnancy. The starting methimazole dose for Graves disease can be based on severity: 5 to 10 mg/d for FT_4 concentrations 1.0 to 1.5 times the upper limit of normal, 10 to 20 mg/d for FT_4 1.5 to 2.0 times the upper limit of normal, and 30 to 40 mg/d for FT_4 2 to 3 times the upper limit of normal.[3] Thyroid function tests should be monitored every 4 to 8 weeks after treatment initiation, and methimazole can often be titrated down to a maintenance dose of 5 to 10 mg/d as hyperthyroidism improves. High-dose methimazole in combination with levothyroxine (a "block and replace" regimen) is not recommended for routine use for patients with Graves disease because the high–antithyroid drug doses required may increase the likelihood of toxicity and a clear benefit has not been established.[48] For patients with autonomous thyroid nodules, methimazole-dose requirements are typically 10 mg/d or less, 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 to 4 months, especially after initiation of antithyroid drugs because dose adjustment is frequently needed.

For patients with Graves disease, antithyroid drug treatment can be discontinued after 12 to 18 months if serum thyrotropin levels have normalized and the patient no longer tests positive for TRAb.[3] TRAb titers typically decline over the course of treatment and resolve in 70% to 80% of patients by 18 months of therapy.[49] Overall, reported remission rates (euthyroidism a year following treatment discontinuation) after an initial 12 to 18 months of antithyroid drug therapy are 30% to 50%,[31,50,51] although the likelihood is much lower (0%-20%) if the patient continues to test positive for TRAb.[3,52] The likelihood of remission may increase with longer duration of treatment, with remission rates up to 80% to 85% reported in selected patients after more than 5 years of antithyroid drug treatment.[51,53] Individuals younger than 40 years with higher thyroid hormone levels at baseline, higher baseline TRAb titers, and larger goiters are less likely to attain remission.[50,54] Hyperthyroidism recurrence is most likely in the first 6 months following antithyroid drug treatment discontinuation, especially if the TRAb level remains elevated. In Graves disease, patients who do not achieve remission after 12 to 18 months or whose hyperthyroidism remits and then recurs, definitive therapy with radioactive iodine or thyroidectomy should be considered.[3] However, methimazole has been shown to be safe and effective for as long as 24 years.[55,56] TRAb titers can be assessed every 1 to 2 years, and thyroid function testing every 4 to 6 months among patients taking antithyroid drug treatment for the long term.[3]

Patients should be carefully counseled about potential adverse effects of antithyroid drugs before treatment initiation. Overall, adverse effects are reported in approximately 13% of patients.[32] The most frequent adverse effect is pruritus and/or rash, occurring in 6% taking methimazole and 3% taking propylthiouracil. Both adverse effects can typically be managed with antihistamines.[3,32]

Table 3. Treatment for Hyperthyroidism Due to Graves Disease and Autonomous Functioning Nodules

Treatment category	Mechanism of action	Efficacy	Adverse effects	Patient factors favoring choice	Patient factors against choice
Antithyroid drugs: methimazole, carbimazole, propylthiouracil	Decrease thyroid hormone synthesis	Short-term (≤12 mo) resolution of hyperthyroidism in nearly all patients, but long-term remission in only 30%-50% of those with Graves disease[30,31]	• Rash in 6%, methimazole; 3%, prophylthiouracil[32] • Agranulocytosis in 0.2%-0.5%[32] • Hepatotoxicity in 2.7% of patients, propylthiouracil; 0.4%, methimazole (rare cases of fulminant hepatic failure with propylthiouracil)[32] • Teratogenicity (17.8/1000, methimazole; 10.2/1000, propylthiouracil)[33] • Possible pancreatitis risk with methimazole (<0.4%)[34] • ANCA vasculitis (methimazole, <1%; propylthiouracil, 3%)[35]	• Desire to avoid permanent hypothyroidism • Current pregnancy • Graves disease with high probability of remission: mild hyperthyroidism, small goiter, and low-titer TRAb • Moderate-severe thyroid eye disease	• Lifelong treatment needed in patients with autonomous thyroid nodules • Greatest risk of relapse in Graves disease
Radioactive iodine	Thyroid tissue destruction	93%[30]	• Cause or exacerbate Graves eye disease in 6%[30] • Possible long-term increased risk of 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[36,37]	• Intolerance of antithyroid drugs • Preference to avoid surgical scar or need for general anesthesia for treatment of autonomous thyroid nodules	• Current pregnancy or lactation or pregnancy planned ≤6 mo • Moderate to severe thyroid eye disease or smoking
Thyroidectomy: total or subtotal	Remove thyroid tissue	99% for total thyroidectomy[30]	• Recurrent laryngeal nerve injury or hypoparathyroidism in 4%-6%[38] • Permanent hypothyroidism in 100% after total thyroidectomy and 14% after lobectomy for autonomous nodule[39]	• Moderate to severe thyroid eye disease • Compressive symptoms from goiter • Known or concern for thyroid malignancy	• Prefers to avoid lifelong need for thyroid hormone replacement therapy after total thyroidectomy • Concern about scar • Lack of access to experienced thyroid surgeon • Comorbidities 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%)[40]	• Overall complication rates 2.4%-3.3% (voice change, nodule rupture, skin burns, brachial plexus injury)[40]	• 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

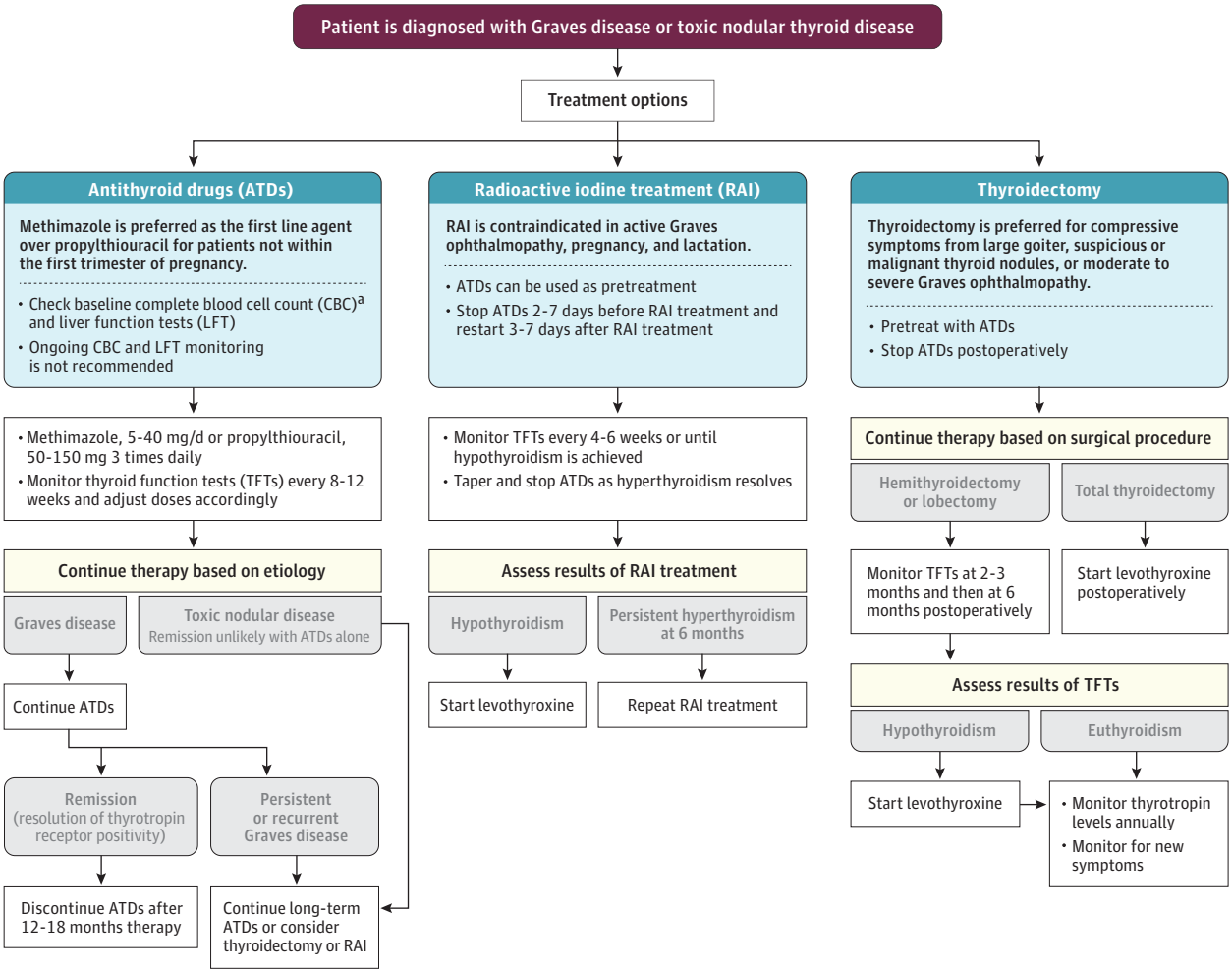
Abbreviations: ANCA, antineutrophilic cytoplasmic antibody; TRAb, thyrotropin receptor antibody.

Successful desensitization protocols have been described for patients allergic to methimazole.[57] Rare adverse effects include agranulocytosis, which occurs in 0.2% to 0.5% of patients and most frequently in the first 90 days after treatment initiation.[58,59] Rare cases of fulminant hepatic failure resulting in death or need for liver transplant have been reported with propylthiouracil use.[60] Both drugs can cause hepatitis. Hepatic injury is reported in approximately 2.7% of patients taking propylthiouracil and 0.4% taking methimazole.[32] Risk of liver injury is highest in the first 90 days after initiating antithyroid drugs.[61] Baseline complete blood cell count and liver function testing is recommended prior to initiating treatment, although it is unclear whether ongoing monitoring is beneficial for patients taking either propylthiouracil or methimazole.[3] Uncontrolled hyperthyroidism is also associated with at least 1 abnormal liver function test result among 55% of patients at baseline, with results normalizing in the majority after treatment initiation, even when baseline transaminases are 5 times the upper limit of normal.[62] Antineutrophil cytoplasmic antibody–associated small-vessel vasculitis has been reported in up to 3% of patients taking antithyroid drugs, with the risk being 3-fold higher with propylthiouracil than with methimazole and increasing with duration of use.[35] In Europe, pancreatitis was recently added as an adverse effect of methimazole, although data for this are conflicting. The absolute risk over the initial 18 months of therapy appears to be less than 0.4%.[34,63]

Radioactive Iodine Treatment

Radioactive iodine treatment cures hyperthyroidism in more than 90% of patients with Graves disease or autonomous thyroid nodules.[30,64] Factors associated with persistent hyperthyroidism after radioactive iodine treatment for Graves disease include male sex, prior antithyroid drug therapy, treatment for more than 6 months after diagnosis, elevated FT_4 levels, larger thyroid volume, and higher radioactive iodine uptake.[65] β-Blockade and pretreatment methimazole are recommended for older patients and for those at particularly high risk of cardiovascular events in case of transiently worsening hyperthyroidism following radioactive iodine treatment.[3] If used, methimazole should be stopped 2 to 7 days prior to treatment and may be restarted 3 to 7 days after treatment.[3,66] The goal of therapy in Graves disease is rendering a patient hypothyroid, whereas in toxic nodular goiter, the goal is to alleviate hyperthyroidism. The eventual likelihood of developing hypothyroidism after radioactive iodine treatment for autonomous thyroid nodules is dependent on the administered activity but may be up to 60%.[36,37] Following radioactive iodine treatment, thyroid function tests should

Figure 2. Treatment of Hyperthyroidism



[a] CBC testing is not to preclude prescription of antithyroid drugs but to have a baseline value so that if questions arise later about possible agranulocytosis on treatment, it is easier to differentiate between effects of the drug and effects of the hyperthyroidism itself.

be measured every 4 to 6 weeks for 6 months or until the patient has become hypothyroid and is stable while taking thyroid hormone replacement therapy. If hyperthyroidism persists after 6 months, repeat radioactive iodine dosing is recommended.[3]

Radioactive iodine may cause or exacerbate eye disease among patients with Graves disease, particularly in those who smoke cigarettes or with very high TRAb titers. To prevent this, pretreatment with prednisone 0.3 mg/kg to 0.5 mg/kg per day, tapered over 3 months, should be used for people who smoke cigarettes, those with high TRAb levels, or those with preexisting thyroid eye disease.[67] Whether radioactive iodine treatment for hyperthyroidism is associated with increased long-term risk of future malignancies is unclear. A recent meta-analysis[68] of 12 studies involving 479 452 people with hyperthyroidism showed no significant association of radioactive iodine exposure with cancer risk compared with nonexposure. However, overall, a linear dose-response association was identified between radioactive iodine therapy and mortality due to breast cancer and other solid tumor cancers.[68]

Thyroid Surgical Procedures

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 ophthalmopathy from Graves disease. Thyroidectomy should be the first-line treatment if concurrent thyroid malignancy is confirmed or suspected.[3] Among patients with Graves disease, total thyroidectomy is associated with a lower risk of recurrent hyperthyroidism than subtotal thyroidectomy and is the preferred operation.[3,69] In individuals with toxic adenoma, thyroid lobectomy may be preferred over radioactive iodine when a rapid resolution is preferred, for cosmesis, or if there are local compressive symptoms from a large thyroid gland.[70] Total thyroidectomy rapidly cures hyperthyroidism from Graves disease or toxic multinodular goiter but results in a lifelong need for thyroid hormone replacement therapy. Potential surgical complications include damage to the recurrent laryngeal nerves, hematoma, and hypoparathyroidism,[71] with higher complication rates for surgeons who have performed relatively few procedures

compared with more experienced surgeons (6.4% vs 4.1%; $P < .001$).[38] Pretreatment with antithyroid drugs lowers the risk of thyroid storm at the time of surgery.[70] Preoperative treatment with high-dose iodine (such as saturated solution of potassium iodide or Lugol solution) for patients with Graves disease decreases thyroid vascularity and thus operative blood loss, although it may not change risks of postoperative complications.[72] Calcium and/or vitamin D supplementation preoperatively may decrease risk of postoperative hypocalcemia.[73]

Novel Treatments

In selected centers, radiofrequency ablation, which induces necrosis of thyroid tissue using heat energy, is a minimally invasive alternative to an operation or to radioactive iodine for treating toxic nodules. This procedure reduces nodule volume by 52% to 86% and normalizes thyroid function in 61.7% (95% CI, 48.7%-74.7%).[40] Guidelines recommend restricting this technique to younger patients with small nodules, although it may be considered for those with larger toxic multinodular goiters who are not candidates for a surgical procedure or radioactive iodine treatment.[74] Novel therapies for Graves disease are currently under investigation, including small molecules, biologics, and immunomodulatory peptides with specific effects at the thyrotropin receptor.[75]

Subclinical Hyperthyroidism

Subclinical hyperthyroidism may resolve spontaneously and may progress to overt hyperthyroidism in approximately 8% of patients by 1 year and 26% by year 5.[76] Progression to overt hyperthyroidism is more common in people with an undetectable serum thyrotropin level at baseline and in those with a toxic multinodular goiter.[76,77] In the US, Black people have lower mean thyrotropin levels than White people. Still, subclinical hyperthyroidism is associated with increased risks of atrial fibrillation, heart failure, total mortality, cardiovascular mortality, and coronary heart disease events.[78,79] Risk of cardiovascular mortality and atrial fibrillation is increased when the serum thyrotropin level is less than 0.1 mIU/L compared with levels in the range of 0.1 to 0.44 mIU/L.[77] Thyroid hormone enhances both osteoblast and osteoclast action, and excess thyroid hormone leads to increased bone resorption.[80] A serum thyrotropin level of 0.1 mIU/L or less has been associated with a 3- to 4-fold increased risk of hip and spinal fracture, especially among postmenopausal women (absolute rates not provided).[81] Subclinical hyperthyroidism has been associated with a 36% increased risk of hip fracture, 28% increased risk of any fracture, and 16% increased risk of nonspine fracture compared with euthyroidism and is associated with low bone density in both men and women.[82]

No placebo-controlled randomized clinical trials have assessed the effects of treatment for subclinical hyperthyroidism. In small and uncontrolled studies, treatment with antithyroid drugs[83] and radioactive iodine[84] has been reported to improve stability of bone density in postmenopausal women. A randomized clinical trial[85] comparing the effects of radioactive iodine therapy with 60 months' treatment with antithyroid drugs in 83 adults 65 years or older with subclinical hyperthyroidism and a baseline serum thyrotropin level of less than 0.1 mIU/L found that by the end of the study, 66% of patients treated with radioactive iodine were hypothyroid and 34% remained euthyroid, whereas 6% of patients treated with antithyroid drugs spontaneously developed hypothyroidism and the other 94% remained euthyroid. 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 US Preventive Services Task Force currently recommends against testing or treatment for subclinical hyperthyroidism.[86] However, other US and European guidelines recommend treatment for subclinical hyperthyroidism when identified in patients older than 65 years (or those ≤65 years old with symptoms, osteoporosis, or heart disease) when the serum thyrotropin level is consistently less than 0.1 mIU/L.[3,87] Therapy can be considered for those groups when the thyrotropin level is persistently in the range of 0.1 to 0.4 mIU/L, but it should be avoided in asymptomatic patients younger than 65 years in the absence of osteoporosis or heart disease. It is also important to consider the possibility of exogenous subclinical hyperthyroidism from excess T_4 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% to 11% of pregnancies and is associated with hyperemesis gravidarum.[88] This condition does not require antithyroid drug treatment and it is not associated with adverse obstetric outcomes.[89] It can simply be monitored with serial thyroid function testing, and it resolves spontaneously as maternal hCG levels decline.[90,91] All other forms of overt hyperthyroidism in pregnancy require treatment to reduce risks for outcomes including preeclampsia, low birth weight, miscarriage, and preterm delivery.[92] Both antithyroid drugs are teratogenic, but congenital anomalies are milder, and risk is lower for propylthiouracil than for methimazole. Propylthiouracil-associated anomalies include facial or neck cysts and urinary tract abnormalities, whereas those associated with methimazole 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 among neonates born to mothers in the methimazole group compared with the control group was 1.28 (95% CI, 1.06-1.54) and for the propylthiouracil group compared with the control group was 1.16 (95% CI, 1.08-1.25; absolute rates were not provided).[93] Therefore, propylthiouracil is preferred in the first trimester of pregnancy.[90,91] Because antithyroid drugs cross the placenta and have more pronounced effects on fetal than on maternal thyroid function, the lowest antithyroid drug dose necessary should be used to maintain the maternal FT_4 level at or just above the upper reference limit.[91] Antithyroid drugs are secreted in breast milk at low levels, but doses up to 20 mg/d of methimazole and 450 mg/d of propylthiouracil are considered safe during lactation and do not require thyroid function monitoring of the breastfed infant.[90] Radioactive iodine treatment is contraindicated during pregnancy and lactation.[91] 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.[91,94] If needed, thyroidectomy in pregnancy is safest in the second trimester.[70]

Thyroid Storm

Thyroid storm consists of severe uncontrolled hyperthyroidism and is characterized by multiorgan system failure and a mortality rate of 3.6% to 17%.[95,96] 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.[96,97] Diagnostic criteria have been published by Burch and Wartofsky[98] and by the Japanese Thyroid Association.[99] Management is aimed at rapidly reducing circulating T_3 levels using antithyroid drugs, glucocorticoids, β-blockade, inorganic iodide, and cholestyramine.[3] Although both drugs decrease thyroid hormone synthesis, US guidelines recommend propylthiouracil for patients with thyroid storm because unlike methimazole, propylthiouracil blocks T_4 to T_3 conversion.[3] However, a recent comparative effectiveness study found no difference in in-hospital mortality, costs, adverse events, or duration of organ support among those treated with propylthiouracil compared with methimazole.[100] In addition to lowering serum T_3 levels, patients should be treated in the intensive care unit and any precipitating illness should be addressed.[3] Plasmapheresis to lower circulating T_3 levels may be considered in refractory cases.[101]

Prognosis

Compared with euthyroidism, overt hyperthyroidism is associated with a 35% to 400% increase in all-cause mortality, varying according to the acuity and severity of hyperthyroidism, and a 20% increase in cardiovascular mortality.[102,103] The exact mechanism is not clear, but increased mortality risks of hyperthyroidism are thought to be related to increased risks of damage to vascular endothelium and hypercoagulability. Mortality is associated with the cumulative duration of time spent hyperthyroid, regardless of the treatment modality used.[104,105] A network meta-analysis[106] that included 3 retrospective studies of patients with Graves disease concluded that although all 3 major treatment modalities were associated with lower risks of congestive heart failure and arrhythmia, surgical removal was associated with greater benefit than were antithyroid drugs or radioactive iodine. Similarly, a registry study[107] involving 10 992 people that compared mortality after treatment for hyperthyroidism concluded that all-cause mortality was lower following surgical removal than after radioactive iodine treatment (absolute rates not provided). A registry-based study reported that all-cause and cardiovascular mortality risk may be higher among patients treated for toxic multinodular goiter than for those treated for Graves disease.[108]

Limitations

This review has several limitations. First, some relevant articles 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 radioactive iodine treatment. Treatment choices should be individualized and patient centered.

ARTICLE INFORMATION

Accepted for Publication: September 4, 2023.

Conflict of Interest Disclosures: Dr Pearce reported receiving honoraria for speaking and travel support from the National Dairy Council, honoraria for speaking at the Merck China Symposium, and travel support for serving as the North American regional coordinator for the Iodine Global Network and serving as member of the American Thyroid Association's task force for the revision of thyroid in pregnancy guidelines. Dr Lee reported serving as a member of the American Thyroid Association's task force for the revision of thyroid in pregnancy guidelines and receiving grants from the National Institute of Environmental Health Science during the conduct of the study and honorarium for speaking from the National Dairy Council outside the submitted work.

Funding/Support: Dr Lee is supported by grant K23ES028736 from the National Institutes of Health and by the Boston University School of Medicine Department of Medicine Career Investment Award.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Mary McGrae McDermott, MD, at mdm608@northwestern.edu.

REFERENCES

1. Taylor PN, Albrecht D, Scholz A, et al. Global epidemiology of hyperthyroidism and hypothyroidism. *Nat Rev Endocrinol*. 2018;14(5):301-316. doi:10.1038/nrendo.2018.18

2. Chung JH. Update on thyroid hormone levels and thyroid dysfunction in the Korean population based on data from the Korea National Health and Nutrition Examination Survey VI (2013 to 2015). *Endocrinol Metab (Seoul)*. 2020;35(1):7-13. doi:10.3803/EnM.2020.35.1.7

3. Ross DS, Burch HB, Cooper DS, et al. 2016 American Thyroid Association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. *Thyroid*. 2016;26(10):1343-1421. doi:10.1089/thy.2016.0229

4. Davies TF, Andersen S, Latif R, et al. Graves' disease. *Nat Rev Dis Primers*. 2020;6(1):52. doi:10.1038/s41572-020-0184-y

5. Nyström HF, Jansson S, Berg G. Incidence rate and clinical features of hyperthyroidism in a long-term iodine sufficient area of Sweden (Gothenburg) 2003-2005. *Clin Endocrinol (Oxf)*. 2013;78(5):768-776. doi:10.1111/cen.12060

6. Laurberg P, Pedersen KM, Vestergaard H, Sigurdsson G. High incidence of multinodular toxic goitre in the elderly population in a low iodine intake area vs high incidence of Graves' disease in the young in a high iodine intake area: comparative surveys of thyrotoxicosis epidemiology in East-Jutland Denmark and Iceland. *J Intern Med*. 1991;229(5):415-420. doi:10.1111/j.1365-2796.1991.tb00368.x

7. Nicholson WK, Robinson KA, Smallridge RC, Ladenson PW, Powe NR. Prevalence of postpartum thyroid dysfunction: a quantitative review. *Thyroid*. 2006;16(6):573-582. doi:10.1089/thy.2006.16.573

8. Rahimi-Bashar F, Vahedian-Azimi A, Dalvand S, et al. Prevalence of amiodarone induced hypothyroidism and hyperthyroidism in patients with heart diseases: a systematic review and meta-analysis. *Curr Med Chem*. 2023;30(23):2690-2699. doi:10.2174/0929867329666220831145651

9. Iwama S, Kobayashi T, Yasuda Y, Arima H. Immune checkpoint inhibitor-related thyroid dysfunction. *Best Pract Res Clin Endocrinol Metab*. 2022;36(3):101660. doi:10.1016/j.beem.2022.101660

10. Muir CA, Tsang VHM, Menzies AM, Clifton-Bligh RJ. Immune related adverse events of the thyroid—a narrative review. *Front Endocrinol (Lausanne)*. 2022;13:886930. doi:10.3389/fendo.2022.886930

11. Ippolito S, Cusini C, Lasalvia P, et al. Change in newly diagnosed Graves' disease phenotype between the twentieth and the twenty-first centuries: meta-analysis and meta-regression. *J Endocrinol Invest*. 2021;44(8):1707-1718. doi:10.1007/s40618-020-01479-z

12. Laurberg P, Jørgensen T, Perrild H, et al. The Danish investigation on iodine intake and thyroid disease, DanThyr: status and perspectives. *Eur J Endocrinol*. 2006;155(2):219-228. doi:10.1530/eje.1.02210

13. Biondi B, Cooper DS. Subclinical hyperthyroidism. *N Engl J Med*. 2018;378(25):2411-2419. doi:10.1056/NEJMcp1709318

14. Green ME, Bernet V, Cheung J. Thyroid dysfunction and sleep disorders. *Front Endocrinol (Lausanne)*. 2021;12:725829. doi:10.3389/fendo.2021.725829

15. Mattesi G, Di Michele S, Mele D, et al. Thyroid dysfunction on the heart: clinical effects, prognostic impact and management strategies. *Monaldi Arch Chest Dis*. 2022;92(4). doi:10.4081/monaldi.2022.2145

16. Mintziori G, Kita M, Duntas L, Goulis DG. Consequences of hyperthyroidism in male and female fertility: pathophysiology and current management. *J Endocrinol Invest*. 2016;39(8):849-853. doi:10.1007/s40618-016-0452-6

17. Dumitriu L, Ursu H. Hyperthyroidism in the elderly, I: clinical manifestations. *Endocrinologie*. 1985;23(2):83-90.

18. Brancatella A, Viola N, Santini F, Latrofa F. COVID-induced thyroid autoimmunity. *Best Pract Res Clin Endocrinol Metab*. 2023;37(2):101742. doi:10.1016/j.beem.2023.101742

19. Viola N, Brancatella A, Sgrò D, Santini F, Latrofa F. Clinical, biochemical features and functional outcome of patients with SARS-CoV-2–related subacute thyroiditis: a review. *Endocrine*. 2023;79(3):448-454. doi:10.1007/s12020-022-03247-w

20. Takedani K, Notsu M, Ishiai N, Asami Y, Uchida K, Kanasaki K. Graves' disease after exposure to the SARS-CoV-2 vaccine: a case report and review of the literature. *BMC Endocr Disord*. 2023;23(1):132. doi:10.1186/s12902-023-01387-2

21. Barajas Galindo DE, Ramos Bachiller B, González Roza L, et al. Increased incidence of Graves' disease during the SARS-CoV2 pandemic. *Clin Endocrinol (Oxf)*. 2023;98(5):730-737. doi:10.1111/cen.14860

22. Bartalena L, Fatourechi V. Extrathyroidal manifestations of Graves' disease: a 2014 update. *J Endocrinol Invest*. 2014;37(8):691-700. doi:10.1007/s40618-014-0097-2

23. de los Santos ET, Starich GH, Mazzaferri EL. Sensitivity, specificity, and cost-effectiveness of the sensitive thyrotropin assay in the diagnosis of thyroid disease in ambulatory patients. *Arch Intern Med*. 1989;149(3):526-532. doi:10.1001/archinte.1989.00390030032006

24. Vasileiou M, Gilbert J, Fishburn S, Boelaert K; Guideline Committee. Thyroid disease assessment and management: summary of NICE guidance. *BMJ*. 2020;368:m41. doi:10.1136/bmj.m41

25. D'Aurizio F. The role of laboratory medicine in the diagnosis of the hyperthyroidism. *Q J Nucl Med Mol Imaging*. 2021;65(2):91-101. doi:10.23736/S1824-4785.21.03344-6

26. Lytton SD, Schluter A, Banga PJ. Functional diagnostics for thyrotropin hormone receptor autoantibodies: bioassays prevail over binding assays. *Front Biosci (Landmark Ed)*. 2018;23(11):2028-2043. doi:10.2741/4687

27. Tozzoli R, Kodermaz G, Villalta D, Bagnasco M, Pesce G, Bizzaro N. Accuracy of receptor-based methods for detection of thyrotropin-receptor autoantibodies: a new automated third-generation immunoassay shows higher analytical and clinical sensitivity for the differential diagnosis of hyperthyroidism. *Auto Immun Highlights*. 2010;1(2):95-100. doi:10.1007/s13317-010-0014-4

28. Favresse J, Burlacu MC, Maiter D, Gruson D. Interferences with thyroid function immunoassays: clinical implications and detection algorithm. *Endocr Rev*. 2018;39(5):830-850. doi:10.1210/er.2018-00119

29. Scappaticcio L, Trimboli P, Keller F, Imperiali M, Piccardo A, Giovanella L. Diagnostic testing for Graves' or non-Graves' hyperthyroidism: a comparison of two thyrotropin receptor antibody immunoassays with thyroid scintigraphy and ultrasonography. *Clin Endocrinol (Oxf)*. 2020;92(2):169-178. doi:10.1111/cen.14130

30. Brito JP, Payne S, Singh Ospina N, et al. Patterns of use, efficacy, and safety of treatment options for patients with Graves' disease: a nationwide population-based study. *Thyroid*. 2020;30(3):357-364. doi:10.1089/thy.2019.0132

31. Sjölin G, Holmberg M, Törring O, et al. The long-term outcome of treatment for Graves' hyperthyroidism. *Thyroid*. 2019;29(11):1545-1557. doi:10.1089/thy.2019.0085

32. Sundaresh V, Brito JP, Wang Z, et al. Comparative effectiveness of therapies for Graves' hyperthyroidism: a systematic review and network meta-analysis. *J Clin Endocrinol Metab*. 2013;98(9):3671-3677. doi:10.1210/jc.2013-1954

33. Morales DR, Fonkwen L, Nordeng HME. Antithyroid drug use during pregnancy and the risk of birth defects in offspring: systematic review and meta-analysis of observational studies with methodological considerations. *Br J Clin Pharmacol*. 2021;87(10):3890-3900. doi:10.1111/bcp.14805

34. Pecere A, Caputo M, Sarro A, et al. Methimazole treatment and risk of acute pancreatitis: a population-based cohort study. *J Clin Endocrinol Metab*. 2020;105(12):dgaa544. doi:10.1210/clinem/dgaa544

35. Balavoine AS, Glinoer D, Dubucquoi S, Wémeau JL. Antineutrophil cytoplasmic antibody-positive small-vessel vasculitis associated with antithyroid drug therapy: how significant is the clinical problem? *Thyroid*. 2015;25(12):1273-1281. doi:10.1089/thy.2014.0603

36. Demir BK, Karakilic E, Saygili ES, Araci N, Ozdemir S. Predictors of hypothyroidism following empirical dose radioiodine in toxic thyroid nodules: real-life experience. *Endocr Pract*. 2022;28(8):749-753. doi:10.1016/j.eprac.2022.05.001

37. Ceccarelli C, Bencivelli W, Vitti P, Grasso L, Pinchera A. Outcome of radioiodine-131 therapy in hyperfunctioning thyroid nodules: a 20 years' retrospective study. *Clin Endocrinol (Oxf)*. 2005;62(3):331-335. doi:10.1111/j.1365-2265.2005.02218.x

38. Adam MA, Thomas S, Youngwirth L, et al. Is there a minimum number of thyroidectomies a surgeon should perform to optimize patient outcomes? *Ann Surg*. 2017;265(2):402-407. doi:10.1097/SLA.0000000000001688

39. Stoll SJ, Pitt SC, Liu J, Schaefer S, Sippel RS, Chen H. Thyroid hormone replacement after thyroid lobectomy. *Surgery*. 2009;146(4):554-558. doi:10.1016/j.surg.2009.06.026

40. Muhammad H, Tehreem A, Russell JO, Tufano RP. Radiofrequency ablation and autonomous functioning thyroid nodules: review of the current literature. *Laryngoscope*. 2022;132(4):906-914. doi:10.1002/lary.29811

41. Lindo A, Breikert A, Lakwijk P, et al. Patient needs and care: moves toward person-centered care for Graves' disease in Sweden. *Eur Thyroid J*. 2023;12(3):e230010. doi:10.1530/ETJ-23-0010

42. Senn JR, Löliger RC, Fischer JGW, Bur F, Maushart CI, Betz MJ. Acute effect of propranolol on resting energy expenditure in hyperthyroid patients. *Front Endocrinol (Lausanne)*. 2023;13:1026998. doi:10.3389/fendo.2022.1026998

43. Brito JP, Castaneda-Guarderas A, Gionfriddo MR, et al. Development and pilot testing of an encounter tool for shared decision making about the treatment of Graves' disease. *Thyroid*. 2015;25(11):1191-1198. doi:10.1089/thy.2015.0277

44. Donovan PJ, McLeod DS, Little R, Gordon L. Cost-utility analysis comparing radioactive iodine, anti-thyroid drugs and total thyroidectomy for primary treatment of Graves' disease. *Eur J Endocrinol*. 2016;175(6):595-603. doi:10.1530/EJE-16-0527

45. Ma EZ, Kuo JH, Malek R, et al. Total thyroidectomy is more cost-effective than radioactive iodine as an alternative to antithyroid medication for Graves' disease. *Surgery*. 2023;173(1):193-200. doi:10.1016/j.surg.2022.06.044

46. Mengistu HS, Getahun KT, Alemayehu L, Gezahign S. Cost-effectiveness analysis of antithyroid drug (propylthiouracil) compared to radioactive iodine for the treatment of Graves' disease in Ethiopia. *Clinicoecon Outcomes Res*. 2022;14:221-229. doi:10.2147/CEOR.S350984

47. Burch HB, Burman KD, Cooper DSA. A 2011 survey of clinical practice patterns in the management of Graves' disease. *J Clin Endocrinol Metab*. 2012;97(12):4549-4558. doi:10.1210/jc.2012-2802

48. Li J, Bai L, Wei F, et al. Effect of addition of thyroxine in the treatment of Graves' disease: a systematic review. *Front Endocrinol (Lausanne)*. 2021;11:560157. doi:10.3389/fendo.2020.560157

49. Laurberg P, Wallin G, Tallstedt L, Abraham-Nordling M, Lundell G, Tørring O. TSH-receptor autoimmunity in Graves' disease after therapy with anti-thyroid drugs, surgery, or radioiodine: a 5-year prospective randomized study. *Eur J Endocrinol*. 2008;158(1):69-75. doi:10.1530/EJE-07-0450

50. Vos XG, Endert E, Zwinderman AH, Tijssen JG, Wiersinga WM. Predicting the risk of recurrence before the start of antithyroid drug therapy in patients with Graves' hyperthyroidism. *J Clin Endocrinol Metab*. 2016;101(4):1381-1389. doi:10.1210/jc.2015-3644

51. Azizi F, Amouzegar A, Tohidi M, et al. Increased remission rates after long-term methimazole therapy in patients with Graves' disease: results of a randomized clinical trial. *Thyroid*. 2019;29(9):1192-1200. doi:10.1089/thy.2019.0180

52. Carella C, Mazziotti G, Sorvillo F, et al. Serum thyrotropin receptor antibodies concentrations in patients with Graves' disease before, at the end of methimazole treatment, and after drug withdrawal: evidence that the activity of thyrotropin receptor antibody and/or thyroid response modify during the observation period. *Thyroid*. 2006;16(3):295-302. doi:10.1089/thy.2006.16.295

53. Park SY, Kim BH, Kim M, et al. The longer the antithyroid drug is used, the lower the relapse rate in Graves' disease: a retrospective multicenter cohort study in Korea. *Endocrine*. 2021;74(1):120-127. doi:10.1007/s12020-021-02725-x

54. Shi H, Sheng R, Hu Y, et al. Risk factors for the relapse of Graves' disease treated with antithyroid drugs: a systematic review and meta-analysis. *Clin Ther*. 2020;42(4):662-675.e4. doi:10.1016/j.clinthera.2020.01.022

55. Villagelin D, Romaldini JH, Santos RB, Milkos AB, Ward LS. Outcomes in relapsed Graves' disease patients following radioiodine or prolonged low dose of methimazole treatment. *Thyroid*. 2015;25(12):1282-1290. doi:10.1089/thy.2015.0195

56. Azizi F, Abdi H, Amouzegar A. Control of Graves' hyperthyroidism with very long-term methimazole treatment: a clinical trial. *BMC Endocr Disord*. 2021;21(1):16. doi:10.1186/s12902-020-00670-w

57. Mazhari A, Emanuele MA, Espiritu B. Desensitization to methimazole. *Endocr Pract*. 2021;27(3):185-190. doi:10.1016/j.eprac.2020.10.019

58. Vicente N, Cardoso L, Barros L, Carrilho F. Antithyroid drug-induced agranulocytosis: state of the art on diagnosis and management. *Drugs R D*. 2017;17(1):91-96. doi:10.1007/s40268-017-0172-1

59. Spratt JS, Greenberg RA. Validity of the clinical alert on breast cancer. *Am J Surg*. 1990;159(2):195-198. doi:10.1016/S0002-9610(05)80258-2

60. FDA drug safety communication: new boxed warning on severe liver injury with propylthiouracil. April 21, 2020. Accessed July 15, 2023. https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/fda-drug-safety-communication-new-boxed-warning-severe-liver-injury-propylthiouracil

61. Yu W, Wu N, Li L, Wang J, OuYang H, Shen H. Side effects of PTU and MMI in the treatment of hyperthyroidism: a systematic review and meta-analysis. *Endocr Pract*. 2020;26(2):207-217. doi:10.4158/EP-2019-0221

62. Scappaticcio L, Longo M, Maiorino MI, et al. Abnormal liver blood tests in patients with hyperthyroidism: systematic review and meta-analysis. *Thyroid*. 2021;31(6):884-894. doi:10.1089/thy.2020.0715

63. Guo JY, Chang CL, Chen CC. Association between thionamides and acute pancreatitis: a case-control study. *Thyroid*. 2020;30(11):1574-1578. doi:10.1089/thy.2019.0589

64. Vija Racaru L, Fontan C, Bauriaud-Mallet M, et al. Clinical outcomes 1 year after empiric 131I therapy for hyperthyroid disorders: real life experience and predictive factors of functional response. *Nucl Med Commun*. 2017;38(9):756-763. doi:10.1097/MNM.0000000000000705

65. Shalaby M, Hadedeya D, Toraih EA, et al. Predictive factors of radioiodine therapy failure in Graves' disease: a meta-analysis. *Am J Surg*. 2022;223(2):287-296. doi:10.1016/j.amjsurg.2021.03.068

66. Zakavi SR, Khazaei G, Sadeghi R, et al. Methimazole discontinuation before radioiodine therapy in patients with Graves' disease. *Nucl Med Commun*. 2015;36(12):1202-1207. doi:10.1097/MNM.0000000000000384

67. Bartalena L, Kahaly GJ, Baldeschi L, et al; EUGOGO †. The 2021 European Group on Graves' Orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Graves' orbitopathy. *Eur J Endocrinol*. 2021;185(4):G43-G67. doi:10.1530/EJE-21-0479

68. Shim SR, Kitahara CM, Cha ES, Kim S-J, Bang YJ, Lee WJ. Cancer risk after radioactive iodine treatment for hyperthyroidism: a systematic review and meta-analysis. *JAMA Netw Open*. 2021;4(9):e2125072. doi:10.1001/jamanetworkopen.2021.25072

69. Guo Z, Yu P, Liu Z, Si Y, Jin M. Total thyroidectomy vs bilateral subtotal thyroidectomy in patients with Graves' diseases: a meta-analysis of randomized clinical trials. *Clin Endocrinol (Oxf)*. 2013;79(5):739-746.

70. Patel KN, Yip L, Lubitz CC, et al. The American Association of Endocrine surgeons guidelines for the definitive surgical management of thyroid disease in adults. *Ann Surg*. 2020;271(3):e21-e93. doi:10.1097/SLA.0000000000003580

71. Cohen O, Ronen O, Khafif A, et al. Revisiting the role of surgery in the treatment of Graves' disease. *Clin Endocrinol (Oxf)*. 2022;96(6):747-757. doi:10.1111/cen.14653

72. Tsai CH, Yang PS, Lee JJ, Liu TP, Kuo CY, Cheng SP. Effects of preoperative iodine administration on thyroidectomy for hyperthyroidism: a systematic review and meta-analysis. *Otolaryngol Head Neck Surg*. 2019;160(6):993-1002. doi:10.1177/0194599819829052

73. Edafe O, Antakia R, Laskar N, Uttley L, Balasubramanian SP. Systematic review and meta-analysis of predictors of post-thyroidectomy hypocalcaemia. *Br J Surg*. 2014;101(4):307-320. doi:10.1002/bjs.9384

74. Papini E, Monpeyssen H, Frasoldati A, Hegedüs L. 2020 European Thyroid Association clinical practice guideline for the use of image-guided ablation in benign thyroid nodules. *Eur Thyroid J*. 2020;9(4):172-185. doi:10.1159/000508484

75. Lane LC, Cheetham TD, Perros P, Pearce SHS. New Therapeutic horizons for Graves' hyperthyroidism. *Endocr Rev*. 2020;41(6):873-884. doi:10.1210/endrev/bnaa022

76. Schouten BJ, Brownlie BE, Frampton CM, Turner JG. Subclinical thyrotoxicosis in an outpatient population—predictors of outcome. *Clin Endocrinol (Oxf)*. 2011;74(2):257-261. doi:10.1111/j.1365-2265.2010.03908.x

77. Vadiveloo T, Donnan PT, Cochrane L, Leese GP. The Thyroid Epidemiology, Audit, and Research Study (TEARS): morbidity in patients with endogenous subclinical hyperthyroidism. *J Clin Endocrinol Metab*. 2011;96(5):1344-1351. doi:10.1210/jc.2010-2693

78. Smedegaard SB, Riis AL, Christiansen MK, Linde JKS. Subclinical hyperthyroidism and the risk of developing cardiovascular disease—a systematic review. *Dan Med J*. 2020;67(11):A12190701.

79. Collet T-H, Gussekloo J, Bauer DC, et al; Thyroid Studies Collaboration. Subclinical hyperthyroidism and the risk of coronary heart disease and mortality. *Arch Intern Med*. 2012;172(10):799-809. doi:10.1001/archinternmed.2012.402

80. Yen PM. Physiological and molecular basis of thyroid hormone action. *Physiol Rev*. 2001;81(3):1097-1142. doi:10.1152/physrev.2001.81.3.1097

81. Kim SM, Ryu V, Miyashita S, et al. Thyrotropin, hyperthyroidism, and bone mass. *J Clin Endocrinol Metab*. 2021;106(12):e4809-e4821.

82. Blum MR, Bauer DC, Collet T-H, et al; Thyroid Studies Collaboration. Subclinical thyroid dysfunction and fracture risk: a meta-analysis. *JAMA*. 2015;313(20):2055-2065. doi:10.1001/jama.2015.5161

83. Mudde AH, Houben AJ, Nieuwenhuijzen Kruseman AC. Bone metabolism during anti-thyroid drug treatment of endogenous subclinical hyperthyroidism. *Clin Endocrinol (Oxf)*. 1994;41(4):421-424. doi:10.1111/j.1365-2265.1994.tb02571.x

84. Faber J, Jensen IW, Petersen L, Nygaard B, Hegedüs L, Siersbaek-Nielsen K. Normalization of serum thyrotrophin by means of radioiodine treatment in subclinical hyperthyroidism: effect on bone loss in postmenopausal women. *Clin Endocrinol (Oxf)*. 1998;48(3):285-290. doi:10.1046/j.1365-2265.1998.00427.x

85. Azizi F, Abdi H, Cheraghi L, Amouzegar A. Treatment of subclinical hyperthyroidism in the elderly: comparison of radioiodine and long-term methimazole treatment. *Thyroid*. 2021;31(4):545-551. doi:10.1089/thy.2020.0433

86. Rugge JB, Bougatsos C, Chou R. Screening and treatment of thyroid dysfunction: an evidence review for the US Preventive Services Task Force. *Ann Intern Med*. 2015;162(1):35-45. doi:10.7326/M14-1456

87. Biondi B, Bartalena L, Cooper DS, Hegedüs L, Laurberg P, Kahaly GJ. The 2015 European Thyroid Association Guidelines on diagnosis and treatment of endogenous subclinical hyperthyroidism. *Eur Thyroid J*. 2015;4(3):149-163. doi:10.1159/000438750

88. Lee SY, Pearce EN. Assessment and treatment of thyroid disorders in pregnancy and the postpartum period. *Nat Rev Endocrinol*. 2022;18(3):158-171. doi:10.1038/s41574-021-00604-z

89. Kinomoto-Kondo S, Umehara N, Sato S, et al. The effects of gestational transient thyrotoxicosis on the perinatal outcomes: a case-control study. *Arch Gynecol Obstet*. 2017;295(1):87-93. doi:10.1007/s00404-016-4219-2

90. Thyroid Disease in Pregnancy. Thyroid disease in pregnancy: ACOG practice bulletin, number 223. *Obstet Gynecol*. 2020;135(6):e261-e274. doi:10.1097/AOG.0000000000003893

91. Alexander EK, Pearce EN, Brent GA, et al. 2017 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. *Thyroid*. 2017;27(3):315-389. doi:10.1089/thy.2016.0457

92. Alves Junior JM, Bernardo WM, Ward LS, Villagelin D. Effect of hyperthyroidism control during pregnancy on maternal and fetal outcome: a systematic review and meta-analysis. *Front Endocrinol (Lausanne)*. 2022;13:800257. doi:10.3389/fendo.2022.800257

93. Agrawal M, Lewis S, Premawardhana L, Dayan CM, Taylor PN, Okosieme OE. Antithyroid drug therapy in pregnancy and risk of congenital anomalies: systematic review and meta-analysis. *Clin Endocrinol (Oxf)*. 2022;96(6):857-868. doi:10.1111/cen.14646

94. Brzozowska M, Roach PJ. Timing and potential role of diagnostic I-123 scintigraphy in assessing radioiodine breast uptake before ablation in postpartum women with thyroid cancer: a case series. *Clin Nucl Med*. 2006;31(11):683-687. doi:10.1097/01.rlu.0000242600.23386.1a

95. Galindo RJ, Hurtado CR, Pasquel FJ, García Tome R, Peng L, Umpierrez GE. National trends in incidence, mortality, and clinical outcomes of patients hospitalized for thyrotoxicosis with and

without thyroid storm in the United States, 2004-2013. *Thyroid*. 2019;29(1):36-43. doi:10.1089/thy.2018.0275

96. de Mul N, Damstra J, Nieveen van Dijkum EJM, et al. Risk of perioperative thyroid storm in hyperthyroid patients: a systematic review. *Br J Anaesth*. 2021;127(6):879-889. doi:10.1016/j.bja.2021.06.043

97. Bourcier S, Coutrot M, Kimmoun A, et al. Thyroid storm in the ICU: a retrospective multicenter study. *Crit Care Med*. 2020;48(1):83-90. doi:10.1097/CCM.0000000000004078

98. Burch HB, Wartofsky L. Life-threatening thyrotoxicosis: thyroid storm. *Endocrinol Metab Clin North Am*. 1993;22(2):263-277. doi:10.1016/S0889-8529(18)30165-8

99. Satoh T, Isozaki O, Suzuki A, et al. 2016 Guidelines for the management of thyroid storm from the Japan Thyroid Association and Japan Endocrine Society (First edition). *Endocr J*. 2016;63(12):1025-1064. doi:10.1507/endocrj.EJ16-0336

100. Lee SY, Modzelewski KL, Law A C, Walkey AJ, Pearce EN, Bosch NA. Comparison of propylthiouracil vs methimazole for thyroid storm in critically ill patients. *JAMA Netw Open*. 2023;6(4):e238655. doi:10.1001/jamanetworkopen.2023.8655

101. Builes-Montaño CE, Rodriguez-Arrieta LA, Román-González A, et al. Therapeutic plasmapheresis for the treatment of thyrotoxicosis: a retrospective multi-center study. *J Clin Apher*. 2021;36(5):759-765. doi:10.1002/jca.21927

102. Sohn SY, Lee E, Lee MK, Lee JH. The association of overt and subclinical hyperthyroidism with the risk of cardiovascular events and cardiovascular mortality: meta-analysis and systematic review of cohort studies. *Endocrinol Metab (Seoul)*. 2020;35(4):786-800. doi:10.3803/EnM.2020.728

103. Dekkers OM, Horváth-Puhó E, Cannegieter SC, Vandenbroucke JP, Sørensen HT, Jørgensen JO. Acute cardiovascular events and all-cause mortality in patients with hyperthyroidism: a population-based cohort study. *Eur J Endocrinol*. 2017;176(1):1-9. doi:10.1530/EJE-16-0576

104. Lillevang-Johansen M, Abrahamsen B, Jørgensen HL, Brix TH, Hegedüs L. Excess mortality in treated and untreated hyperthyroidism is related to cumulative periods of low serum TSH. *J Clin Endocrinol Metab*. 2017;102(7):2301-2309. doi:10.1210/jc.2017-00166

105. Okosieme OE, Taylor PN, Evans C, et al. Primary therapy of Graves' disease and cardiovascular morbidity and mortality: a linked-record cohort study. *Lancet Diabetes Endocrinol*. 2019;7(4):278-287. doi:10.1016/S2213-8587(19)30059-2

106. Issa PP, Hussein M, Omar M, et al. Cardiovascular health by Graves' disease management modality—surgery versus radioactive iodine versus antithyroid medications: a network meta-analysis. *J Surg Res*. 2023;283:266-273. doi:10.1016/j.jss.2022.10.043

107. Giesecke P, Frykman V, Wallin G, et al. All-cause and cardiovascular mortality risk after surgery versus radioiodine treatment for hyperthyroidism. *Br J Surg*. 2018;105(3):279-286. doi:10.1002/bjs.10665

108. Giesecke P, Rosenqvist M, Frykman V, et al. Increased cardiovascular mortality and morbidity in patients treated for toxic nodular goiter compared to Graves' disease and nontoxic goiter. *Thyroid*. 2017;27(7):878-885. doi:10.1089/thy.2017.0029