Review Article

Hyperthyroidism

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Abstract: Hyperthyroidism is a condition where the thyroid gland produces and secretes inappropriately high amounts of thyroid hormone which can lead to thyrotoxicosis. The prevalence of hyperthyroidism in the United States is approximately 1.2%. There are many different causes of hyperthyroidism, and the most common causes include Graves' disease (GD), toxic multinodular goiter and toxic adenoma. The diagnosis can be made based on clinical findings and confirmed with biochemical tests and imaging techniques including ultrasound and radioactive iodine uptake scans. This condition impacts many different systems of the body including the integument, musculoskeletal, immune, ophthalmic, reproductive, gastrointestinal and cardiovascular systems. It is important to recognize common cardiovascular manifestations such as hypertension and tachycardia and to treat these patients with beta blockers. Early treatment of cardiovascular manifestations along with treatment of the hyperthyroidism can prevent significant cardiovascular events. Management options for hyperthyroidism include anti-thyroid medications, radioactive iodine, and surgery. Anti-thyroid medications are often used temporarily to treat thyrotoxicosis in preparation for more definitive treatment with radioactive iodine or surgery, but in select cases, patients can remain on antithyroid medications long-term. Radioactive iodine is a successful treatment for hyperthyroidism but should not be used in GD with ophthalmic manifestations. Recent studies have shown an increased concern for the development of secondary cancers as a result of radioactive iodine treatment. In the small percentage of patients who are not successfully treated with radioactive iodine, they can undergo re-treatment or surgery. Surgery includes a total thyroidectomy for GD and toxic multinodular goiters and a thyroid lobectomy for toxic adenomas. Surgery should be considered for those who have a concurrent cancer, in pregnancy, for compressive symptoms and in GD with ophthalmic manifestations. Surgery is cost effective with a high-volume surgeon. Preoperatively, patients should be on anti-thyroid medications to establish a euthyroid state and on beta blockers for any cardiovascular manifestations. Thyroid storm is a rare but life-threatening condition that can occur with thyrotoxicosis that must be treated with a multidisciplinary approach and ultimately, definitive treatment of the hyperthyroidism.

Keywords: Hyperthyroidism; Graves' disease (GD); toxic multinodular goiter; toxic adenoma; surgery; radioactive iodine (RAI)

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Introduction

Hyperthyroidism is defined as an inappropriately high synthesis and/or secretion of thyroid hormones from the thyroid gland. Thyrotoxicosis is the clinical condition where the effect of excess thyroid hormone on the tissues causes systemic clinical manifestations (1). The prevalence of hyperthyroidism in the United States is 1.2% with overt hyperthyroidism accounting for 0.5% and subclinical hyperthyroidism accounting for 0.7% (1-3). In this review, we will discuss the causes of hyperthyroidism, the clinical manifestations and how to diagnose it, and the different management options for the most common types of hyperthyroidism, including thyroid storm (TS), a rare but serious complication of hyperthyroidism.

Causes

The most common causes of hyperthyroidism are Graves' disease (GD), followed by toxic multinodular goiters (TMNG) and toxic adenomas (TA). GD is an autoimmune condition that occurs with the loss of immunotolerance causing thyrotropin receptor antibodies (TRAb) to form, bind and subsequently stimulate the thyroid stimulating hormone (TSH) receptors. This causes increased thyroid hormone synthesis and secretion (4). Non-toxic nodular goiters can sporadically develop and become autonomous overtime causing hyperthyroidism (5). These conditions demonstrate autonomous hormone production, which can be from mutations of genes that regulate thyroid hormone synthesis or the TSH receptor causing familial and sporadic non-autoimmune hyperthyroidism (6). The prevalence of TAs and TMNGs increases with age and iodine deficiency (1).

Other causes of hyperthyroidism include iodine-induced, TSH-producing pituitary tumors, trophoblastic and germ cell tumors, struma ovarii, thyroid cancer, silent or painless thyroiditis from pregnancy or medications such as lithium or tyrosine kinase inhibitors, painful thyroiditis from infections, amiodarone-induced thyroiditis, and exogenous thyroid hormone intake (1,4,7,8). Hyperthyroidism in pregnancy can be overt hyperthyroidism, most commonly from GD (4), or subacute thyroiditis in the post-partum period. This type of thyrotoxicosis is usually self-limited followed by a period of hypothyroidism and then recovery of thyroid function (9). Therefore, anti-thyroid medications and radioactive iodine (RAI) treatment are not recommended. Painless or postpartum thyroiditis can recur in subsequent pregnancies so these patients should have continued monitoring. Painful thyroiditis is typically from an infection and is self-limited. Treatment can include beta blockers for symptoms associated with any thyrotoxicosis, non-steroidal anti-inflammatories and steroids for severe cases.

Amiodarone-induced thyroiditis can present as either type I or type II (4). Type I occurs from underlying TMNG or GD that are exposed to high iodine content from amiodarone causing excess thyroid hormone production. Treatment includes anti-thyroid medications and potassium perchlorate. Type II is a destructive thyroiditis from the toxicity of amiodarone on thyroid cells. It is usually self-limited, may not require discontinuation of amiodarone, and treatment includes steroids or surgery for refractory disease.

Presentation and diagnosis

Biochemical

TSH is the most sensitive and specific first-line biochemical test to examine thyroid function (10). Confirmatory testing with free T4 and total serum T3 can be done for high suspicion of thyrotoxicosis or to further evaluate an abnormal TSH level. Some laboratory protocols add on a free T4 and total T3 when the initial TSH is low to avoid subsequent phlebotomy. Overt hyperthyroidism will show low TSH and high T3/T4 levels while subclinical hyperthyroidism will show low TSH with normal T3/T4 levels. GD will usually have positive TRAbs (1).

A ratio of the total T3 to total T4 can be calculated to help distinguish the etiology of thyrotoxicosis. Overt hyperthyroidism will produce more T3, creating a high T3:T4 ratio. Thyroiditis will have higher T4 levels creating a low T3:T4 ratio (11). Exogenous ingestion of thyroid hormone will present with low thyroglobulin levels, which is released from the thyroid gland with thyroid hormones, and a low T3:T4 ratio.

Other more rare etiologies can cause abnormal thyroid function tests. Euthyroid hyperthyroxinemia can occur in certain circumstances when the free T4 and total T3 are high, without a low TSH, due to abnormal protein binding (pregnancy, estrogen therapy, hepatitis, acute intermittent porphyria, medications or drug abuse, and high altitudes) (12). High doses of biotin can interfere with assays and cause falsely elevated T4 levels because biotin competes with biotinylated analogues in the binding assay. Patients should stop biotin for at least 2 days before having TSH and T4 tested (1).

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While thyroid function tests can confirm a diagnosis of hyperthyroidism, it doesn't necessarily clarify the etiology. A clinical diagnosis of GD can be made if the thyroid gland is diffusely enlarged, there is moderate to severe thyrotoxicosis, and Graves' ophthalmopathy (GO) is present. If the clinical diagnosis is not clear due to lack of GO, a TRAb level can be obtained and a positive TRAb confirms the diagnosis. If the TRAb is negative or unclear, a RAI uptake (RAIU) scan can be done to distinguish GD from other etiologies (1). Studies have shown that in the United States, testing TRAb over RAIU reduces costs and gives a faster diagnosis (13). Patients with autoimmune causes of their hyperthyroidism often will have thyroid peroxidase antibodies as well.

Clinical

The clinical manifestations of hyperthyroidism can be diverse as thyroid hormones can have an impact on a variety of systemic symptoms. The cellular effects of T3 binding to alpha and beta receptors increases thermogenesis and basal metabolic rates. This can result in constitutional symptoms of weight loss, fatigue and heat intolerance. Skin changes can occur including warm, moist skin with thinning of hair and pretibial myxedema in GD. Musculoskeletal manifestations include weakness, increased bone resorption, osteoporosis and increased risk of fracture. Patients can develop lymphadenopathy, gynecomastia in men or oligomenorrhea in women. Gastrointestinal (GI) manifestations include dysphagia, hyperdefecation and hunger (7). Ophthalmologic findings include lid retraction and infiltrative GO can be seen in patients with GD (1,14). Older age, smoking, longer duration of symptoms and female gender are risk factors associated with GO (15).

Significant cardiovascular manifestations are common in hyperthyroidism and it is important to recognize and treat them appropriately (7). The most common cardiovascular manifestations of hyperthyroidism are hypertension (HTN) and tachycardia. Approximately, 10% of the total population has HTN from secondary causes including endocrine etiology, and HTN may be the first presentation of a primary endocrine pathology (8). The pathophysiology of HTN with hyperthyroidism is multifaceted. Under normal conditions, the tissue effects of T3 are important for homeostasis. Problems occur when T3 is in excess because it directly increases cardiac contractility and (8,16) dilates arterioles, which decreases systemic vascular resistance and arterial filling. In turn, this stimulates renin release and activation of the angiotensin-aldosterone axis (17). Additionally, thyroid hormone targets certain ion channels including calcium/calmodulin-dependent kinase IV which plays a role in endothelial nitric oxide synthase activity contributing to control of vascular tone and blood pressure regulation (8,18,19). Thus, thyrotoxicosis is associated with arterial stiffness (20). Thyroid hormone excess also causes higher levels of atrial natriuretic peptide, brain natriuretic peptide, endothelin-1, vasodilating polypeptide adrenomedullin, and erythropoietin which all effect hemodynamics (8,16,21,22).

The clinical presentation will be HTN, tachycardia, and increased cardiac output which is similar in presentation to increased adrenergic activity, yet catecholamines may be low or normal in hyperthyroidism (22,23). Atrial fibrillation and congestive heart failure (CHF) can occur as well. Older age, higher T4 levels, male gender and toxic nodules are associated with a risk of atrial fibrillation. Early studies show that heart failure develops in 6–16% of patients with hyperthyroidism, but even higher rates are expected if there is underlying cardiovascular disease (8). Atrial fibrillation is an independent risk factor for developing heart failure (24). These cardiovascular manifestations can be reversible following treatment of hyperthyroidism and achieving a euthyroid state (24,25).

Treatment of cardiovascular manifestations should be in conjunction with treatment of the hyperthyroidism. Studies show that patients with untreated or insufficiently treated hyperthyroidism, compared to those who are treated, are at significantly higher risk of adverse cardiovascular events. Timely treatment and careful monitoring of hyperthyroid patients can help to reduce this risk (26). The recommended treatment for patients with hyperthyroidism is to block the cardiovascular effects with beta blockers. If there is a contraindication to beta blockers, angiotensin-converting enzyme (ACE)-inhibitors or calcium-channel blockers can be used (8,27).

There is evidence that subclinical hyperthyroidism can increase the risk of cardiovascular events, yet it has not necessarily been proven to be associated with HTN. Nonetheless, many authors recommend treatment of subclinical hyperthyroidism to prevent cardiovascular risk, among other reasons (8,28).

Imaging

Once biochemical and clinical features have been identified, imaging modalities such as ultrasound and RAIU scans

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play an important role in diagnosis and treatment planning. A RAIU scan can distinguish between GD and TAs or TMNGs. In GD, the scan will show diffuse RAIU throughout the gland. A TMNG will show irregular patterns of uptake and a TA will show a localized area of uptake with no uptake in the remaining gland (4). In certain conditions when there is an acute release of excess thyroid hormone but no ongoing overproduction, there will be no RAIU. These conditions include painless thyroiditis, amiodarone-induced thyroiditis, subacute thyroiditis, palpation (surgical manipulation) thyroiditis, iatrogenic thyrotoxicosis, factitious ingestion of thyroid hormone, struma ovarii, and metastatic disease from follicular thyroid cancer (1).

Ultrasound with the use of color flow doppler can be an alternative method to help with the diagnosis, especially when a RAIU scan is contraindicated (pregnancy, breast feeding, allergies). In expert hands, the thyroidal blood flow can be measured and can help distinguish between GD which will show diffuse increased blood flow, thyroiditis which may show patchy areas of increased flow (29,30), or a toxic nodule which will show nodular disease with a normal thyroid in the background.

Management

The treatment options for hyperthyroidism are based on the cause and include medical management with beta blockers or anti-thyroid medication, RAI and surgery. For GD, the most recent 2016 American Thyroid Association (ATA) Guidelines consider RAI, anti-thyroid medications or surgery all reasonable effective options. For TAs and TMNGs, RAI and surgery are typically recommended with anti-thyroid medications used only for short-term management (1). Each treatment modality has advantages and disadvantages that need to be considered. These options are preference-sensitive meaning that the patient and provider must discuss the tradeoffs for each individual (31).

Anti-thyroid and other medications

Generally, anti-thyroid medications are used as a bridging therapy to establish euthyroidism in preparation for a definitive treatment such as RAI or surgery (7). Patients that wish to avoid the risks of surgery or RAI may choose long-term anti-thyroid medications. However, the risks of anti-thyroid medication include potential serious side effects, risk of relapse or persistent hyperthyroidism, lack of definitive treatment, and a longer interval to establish a euthyroid state.

The primary anti-thyroid medications are propylthiouracil (PTU) and methimazole. They don't demonstrate peak efficacy for 4–6 weeks, so most patients need beta blockers for immediate symptomatic relief of thyrotoxicosis. Beta blockers are recommended in all patients with symptomatic thyrotoxicosis, elderly patients, and those with tachycardia or co-existing cardiovascular disease (1). Beta blockers are contraindicated in patients with bronchospastic asthma, and in such cases ACE-inhibitors or calcium-channel blockers (diltiazem, verapamil) can be used (8,27). Beta blockers inhibit the conversion of T4 to T3 while controlling tachycardia and tremor. Propranolol is the most commonly used medication and is dosed at 10–40 mg 4 times a day (7).

Methimazole is recommended as first-line treatment, except during pregnancy when PTU is preferred due to the teratogenic effects of methimazole. Methimazole is generally preferred due to better efficacy (32), longer half-life and duration of action (4,33) allowing for once a day dosing, and less side effects compared to PTU. Methimazole is started at 10–30 mg daily and PTU is started at 100 mg 3 times daily (7). Methimazole inhibits the early step in thyroid hormone synthesis by inhibiting thyroid peroxidase (34), and also may inhibit thyroglobulin synthesis (35). PTU inhibits new hormone synthesis but also decreases the conversion of T4 to T3 in the periphery (34).

When starting anti-thyroid medications, it is recommended to obtain a baseline set of labs to check complete blood count and liver enzymes due to the potential side effects, which are overall rare. Common minor side effects include fever, rash, pruritus, hair loss, lymphadenopathy, headache, myalgias and arthralgias. More severe side effects include agranulocytosis, hepatotoxicity, vasculitis, lupus-like syndrome, and neuritis (7,34). It is recommended to check a free T4 and T3 at 2–6 weeks after initial therapy and adjust dosing according to the levels. It is not recommended to check TSH because it may remain suppressed for months (1,7). Once euthyroidism is achieved, the dose can be decreased by 30–50% with continued monitoring every 4–6 weeks (1). Additional white blood cell counts should be obtained in any febrile patients, and a liver panel should be sent in any patients who develop jaundice, pruritic rash, dark urine, light stools, joint or abdominal pain. There are no recommendations for routine

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monitoring of these labs once established on anti-thyroid medications, so it is provider preference (1).

Anti-thyroid medications should be discontinued after 12–18 months if a patient is considered in remission with normal TSH and TRAb (in the case of GD) (1,4,34). Remission can be defined by normal thyroid function tests after 1 year. Approximately, half of patients taking anti-thyroid medications will enter remission but this can vary from 30% to 70% depending on clinical and geographical population factors (34,36). Once a patient is able to stop their anti-thyroid medication, the ATA guidelines recommend thyroid function tests to be monitored every 2–3 months for the 1st 6 months, every 4–6 months for the next 6 months and then every 6–12 months (1).

Patients need to be educated about symptoms of hyperthyroid returning in relapse, which can happen years later (1). Higher doses of anti-thyroid medications and longer courses of treatment do not increase the chance of remission, but only increase side effects, so this practice is not recommended (1,37,38). In GD, TRAb levels prior to discontinuing the medication may predict which patients can be successfully weaned. Those more likely to relapse are younger, have severe disease with large goiters, high T3/T4 levels, persistent suppression of TSH (4,39), high baseline levels of TRAb (40) or persistent elevated TRAbs and should be considered for definitive treatment with RAI or surgery (1,41). Continued low dose anti-thyroid medical treatment can be considered in mild disease or with contraindications to definitive treatment. A recent analysis of patients who relapsed after medical treatment compared follow up RAI ablation versus continued medical therapy and found the medical therapy group had less GO, less persistent thyroid disfunction, and less weight gain (42). In select patients, the authors of some studies have found long-term anti-thyroid medication treatment to be safe (43).

RAI

Advantages of RAI include avoidance of surgical risk and potential avoidance of hormone replacement therapy. Yet, the disadvantages include a risk of treatment failure and persistent hyperthyroidism requiring either re-treatment with more RAI or subsequent surgery and a longer interval to reach a euthyroid or hypothyroid state (44). RAI treatment should be considered in the elderly, those with significant co-morbidities, contraindications for surgery, previous neck radiation, small goiters, and limited access to high volume surgeons (1). It is contraindicated in pregnancy or those planning a pregnancy and in those who cannot comply with radiation safety guidelines. RAI should be used with extreme caution in GD as it can exacerbate GO (45,46). RAI treatment with steroids can be considered in the absence of GO and in mild GO in non-smokers, but it should be avoided in moderate to severe GO (1).

Clinical exacerbation of hyperthyroidism and even TS can occur with RAI, especially in the elderly and those who have comorbidities that may increase the risk of thyrotoxicosis (47,48) including cardiovascular disease, atrial fibrillation, heart failure, pulmonary HTN, diabetes, renal failure, infection, trauma, or cerebrovascular disease. These patients should be given beta blockers (1,21,49) and be considered for methimazole treatment before and after RAI treatment. In individuals who will benefit from pre-treatment with methimazole, the recommendation is to give it prior to RAI but discontinue it 2–3 days prior to RAI treatment, and then resume 3–7 days after RAI treatment with a taper while thyroid function tests should simultaneously normalize. Young healthy individuals who are clinically well compensated should be able to tolerate RAI without pre-treatment (1). In patients who are not pre-treated, thyroid levels should stabilize or decrease in the first month after RAI (50).

A typical average dose of RAI is 10–15 mCi. The dose can be given in a fixed dose or calculated based on the RAIU by the thyroid gland and the size of the gland with comparable successful treatment outcomes (51). A pregnancy test should be done prior to treating. Dosing must be carefully considered in patients on dialysis and with jejunostomy or gastric feeding tubes. It is recommended to avoid high iodine diets and foods for 1 week prior to treatment (1).

After RAI treatment, it is recommended to recheck thyroid function tests within 1–2 months. Monitoring should be continued every 4–6 weeks for at least 6 months or until achievement of hypothyroidism with a stable dose of thyroid hormone replacement. Most patients respond to treatment in 4–8 weeks, meaning clinical symptoms improve and thyroid function tests are normalized or even show a hypothyroid state. Starting thyroid hormone replacement depends on thyroid function tests and clinical symptoms. Patients are biochemically hypothyroid when their free T4 is below normal. Thus, thyroid hormone replacement therapy can be instituted at that time with further adjustments based on continued free T4 monitoring. TSH levels may be suppressed for months, so this lab should not be used to determine the timing of initiation of thyroid

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hormone replacement (7). Beta blockers can be tapered and other medical therapy can be stopped after successful RAI treatment.

The success rate of RAI varies depending on the definition of success, the etiology of hyperthyroidism and the dose given. Thankfully, RAI treatment for the 3 most common causes of hyperthyroidism is generally successful. One study evaluated RAI treatment in GD, TA, and TMNG. The authors reported successful RAI treatment, defined as subsequent hypothyroid or euthyroid state, to be 87.1% in GD, 93.7% in TA and 81.1% in TMNG (52). For patients with GD who are unresponsive to RAI, have persistent enlarged glands, higher T4 levels or continued symptoms of hyperthyroidism, re-treatment with a higher dose of RAI can be considered at 6 months (3 months in select patients) (1). The goal of re-treatment should be hypothyroidism (1) and some authors recommend re-treatment with a higher dose of RAI (53). One single-institution study found a RAI failure rate of 23% and reported certain predictors of failure to be more severe tachycardia at presentation, more severe laboratory abnormalities, and low doses of RAI <13 mCi (54). This was consistent with other literature regarding dosing (53). Providers often lack selection criteria between RAI and surgery for follow-up treatment after failed RAI, other than the known contraindications for either (55). Often times patients are referred to surgeons after RAI has failed, however surgery after fibrosis caused by RAI can be more challenging.

RAI and cancer risk

Postoperative RAI for thyroid cancer has been shown to increase the risk of second primary malignancies, including bone, leukemia, soft tissue sarcomas, salivary gland and GI tract as these doses are usually >100 mCi (56,57). Studies have been inconclusive for the risk of developing site-specific cancers after treatment with RAI for hyperthyroidism (56,58-60). Doses of RAI are much less (10–15 mCi) for hyperthyroidism compared to postoperative cancer treatment, and absorption of radiation varies in different organs (1,56). However, given the significant retained uptake within the thyroid gland in hyperthyroidism, the total body radiation exposure may actually be higher in treatment for hyperthyroidism versus cancer.

In 1998, the Cooperative Thyrotoxicosis Therapy Follow-up Study Group determined RAI did not contribute to an increased risk of total cancer mortality and was safe (61). More recent studies however, have shown mixed results. Some authors report a higher incidence of stomach, kidney and breast cancers in those who underwent RAI ablation for hyperthyroidism (58). Others show no increase in overall cancer risk, but suspect trends towards increased risk in thyroid, kidney, stomach and respiratory tract cancers. The Cooperative Thyrotoxicosis Therapy Follow-up Study Group has been extended an additional 24 years to examine the radiation dose-response relationships for site-specific cancer death within the group of hyperthyroid patients who were treated with RAI (56), and this study does now confirm an increased risk of secondary cancers (including breast) due to RAI treatment for hyperthyroidism. This study included patients with hyperthyroidism in 25 United States medical centers and 1 United Kingdom center between 1946 and 1964 (56,62) with a total 18,805 patients analyzed. The average administered RAI activity was 10.1 mCi for GD and 17.6 mCi for TMNG. The authors found that the relative risk of death from solid organ cancers (including breast) increases with greater doses of RAI. In summary they found if patients are treated for hyperthyroidism at age 40, 1 in 31–52 patients would develop a secondary cancer, and of those treated at age 50, 1 in 32–55 would develop a secondary cancer (56). This study may shift the decision-making process going forward with regards to definitive treatment, especially as the number of high-volume endocrine surgeons continues to increase (63).

Surgery

Advantages of surgery for hyperthyroidism allow for nearly 100% cure rates, identification of incidental cancers, and rapid achievement of euthyroid or hypothyroid states (1). Disadvantages are perioperative and postoperative risks of thyroid surgery including bleeding, hypocalcemia, recurrent laryngeal nerve injuries, and the potential need for lifelong thyroid hormone replacement. Surgery should be considered if there are compressive symptoms, suspicion for or known thyroid cancer, concurrent hyperparathyroidism, large or substernal goiters, low RAIU, in pregnancy planning, pregnancy in the 2nd trimester, GD with GO, or the need for fast definitive therapy in thyrotoxicosis (44).

Surgery, when done by a high-volume surgeon, is the most cost-effective definitive treatment for GD (64), TA, and TMNG with failure rates <1% (1). Total thyroidectomy is recommended for GD and TMNG. TAs on the other

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hand, should undergo ultrasound evaluation to assess the entire thyroid gland. If feasible, a lobectomy can be done for isolated TAs (1). This offers the advantage of potentially avoiding hormone replacement therapy. Preoperatively, patients should be on anti-thyroid medications to establish a euthyroid state. Beta blockade should be initiated for higher risk individuals including elderly, severe thyrotoxicosis, and existing cardiovascular disease (4). In the setting of GD (not TA or TMND), inorganic iodide administration preoperatively in the form of saturated potassium iodide solutions (SSKI) or potassium iodide-iodine (Lugol's solution) is also recommended (7). It will decrease blood flow to the thyroid, decrease intraoperative blood loss and has been shown to improve the safety of surgery with decreased rates of transient hypoparathyroidism and hoarseness from transient recurrent laryngeal nerve injury (65).

The main risks of surgery include anesthesia, bleeding, hypocalcemia with hypoparathyroidism, and recurrent laryngeal nerve injury. These risks, however, remain very low with high-volume surgeons, which some authors define as >100 thyroid surgeries per year (66,67). Risk of recurrent laryngeal nerve injury remains <1% and transient hypocalcemia <10% (44). In GD, preoperative vitamin D deficiency, female gender, and perioperative parathyroid autotransplantation have been shown to be predictors for post-thyroidectomy hypocalcemia (68,69). Therefore, the authors recommend preoperative and postoperative supplementation with calcium carbonate and activated vitamin D if needed, to decrease rates of postoperative hypocalcemia (70). Additional advantages of surgery may apply to those of lower socioeconomic status and those with weight concerns. One study has shown that in their institution's population of patients, those with a lower socioeconomic status had more features of GD to make surgery more favorable (71). Another study found that patients who undergo surgery as first line treatment for hyperthyroidism are less likely to become obese or gain weight postoperatively (72).

Postoperatively, anti-thyroid medications and iodide solutions can be stopped and beta blockers should be weaned off. For patients undergoing a total thyroidectomy, thyroid hormone replacement should be started on a weight based or body mass index (BMI) based calculation, typically between 1.2–1.8 μg/kg/day (73). For both total thyroidectomy and lobectomy, TSH should be measured by 6–8 weeks postoperatively to assess remaining thyroid function or the dosing of thyroid hormone replacement. About 75% of patients will require subsequent dose adjustments before they are euthyroid (74). Patients can experience undesirable symptoms of hyper or hypothyroidism during this dose adjustment period, and therefore it is important to achieve a euthyroid state in these patients as soon as possible. Recent studies are identifying algorithms using machine learning and TSH values that can assist in these subsequent dose changes (75). TSH should be measured every 1–2 months until stable, and then every year.

When thyroid nodules are found in patients with GD, they should be managed according to guidelines and recommendations for euthyroid cases (76,77). There is an increased risk of cancer in GD, typically of papillary variant. This may be due to increasingly sensitive preoperative evaluation modalities or increased incidental findings of microcarcinoma in surgical specimens. Nonetheless, a recent international meta-analysis found that the incidence is likely at least 2 times higher than the previous reported rate of 2% (78). If a nodule is suspicious or proven to be cancer, the recommended treatment for the hyperthyroidism is surgery. In summary, surgical treatment for GD, TA and TMNG is a safe option for surgical candidates with high-volume surgeons.

Thyroid storm

TS is a rare, potentially life-threatening condition that occurs in thyrotoxicosis leading to multiple organ system decompensation that is usually triggered by severe stress (79) with a mortality rate ranging 8–25% (80). Clinical presentation of TS includes thyrotoxicosis with a goiter most commonly from GD, fever, cardiopulmonary dysfunction (tachycardia, CHF), central nervous system (CNS) manifestations (finger tremor, restlessness, psychosis, lethargy, coma), and GI-hepatic dysfunction (nausea, emesis, diarrhea, abdominal pain, jaundice) (79). Many different triggers have been identified, with the most common being non-compliance with anti-thyroid medications or infection (79,81). Other predisposing conditions causing major systemic stress include trauma, non-thyroid surgery, direct pressure from thyroid surgery or strangulation (82), RAI therapy (1), acute illness such as sepsis or diabetic ketoacidosis (83), and pregnancy or child birth (4).

Diagnosis of TS is clinical and not always clear, but several diagnostic aids are available. Burch-Wartofsky scores (BWS) identify criteria with a scoring system that allocates points for various system dysfunctions including

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thermoregulatory, CNS, GI-hepatic and cardiovascular. A score of <25 points is low suspicion for TS, a score of 25–44 points allocates impending TS and a threshold of ≥45 points is highly suggestive of TS (80,84). The Japanese Thyroid Association recognizes different diagnostic criteria formulated from a retrospective study by Akamizu *et al.* that suggested TS1 and TS2 diagnostic criteria. It differs from BWS in that thyrotoxicosis was a prerequisite for diagnosis and they did not use a scoring system, but rather a combination of clinical features for diagnosis: thyrotoxicosis with different combinations of CNS manifestations, fever, tachycardia or CHF, and GI-hepatic dysfunction (79). Comparisons of the diagnostic criteria may suggest the TS1/TS2 criteria is not as sensitive as BWS for diagnosing TS (80).

Treatment of TS requires multiple modalities. According to the BWS scores, patients in the intermediate category of 25–44 points should be monitored closely and treated based on provider discretion. Patients with 45 points or more should absolutely be treated. Treatment strategies should include blocking thyroid hormone synthesis and secretion, blocking the peripheral effects of thyroid hormone, reversing systemic hemodynamic decompensation, treating the precipitating stressor and definitive therapy (1,84). Several ways to decrease thyroid hormone include PTU as it blocks the synthesis of new hormone and the conversion from T4 to T3 in the periphery (34,85), glucocorticoids (86), and beta blockers, specifically propranolol (87). Lugol's solution or SSKI should be given to further rapidly decrease both T3 and T4 levels (88). ATA guidelines recommend the following dosing: PTU 500–1,000 mg load and then 250 mg every 4 hours. Propranolol 60–80 mg every 4 hours. Hydrocortisone 300 mg intravenous load and then 200 mg every 8 hours. SSKI is given orally as 5 drops (0.25 mL or 250 mg) every 6 hours (1). In a worst case scenario when patients are unresponsive to the above treatment, plasma pheresis can be done. Decompensated hemodynamics in critically ill patients with TS can initiate many of the secondary clinical features seen and thus, optimizing cardiovascular function and hemodynamics with aggressive volume resuscitation is of utmost importance (80). Cooling blankets and acetaminophen can be administered for fever. Respiratory, nutritional and intensive care unit support should be given if needed. Definitive treatment includes surgery or RAI, but patients should be recovered from the acute decompensation of TS and be as close to euthyroid as possible before initiating this definitive treatment (4).

Conclusions

In summary, hyperthyroidism is a complex pathology with many etiologies in which multiple diagnostic modalities can be utilized to identify the best treatment. The treatment of choice is preference-sensitive and should involve a shared decision-making process between the patient and provider. Thus, patient education is important so that each individual understands their options and can choose the treatment that best addresses their concerns. Successful treatment of hyperthyroidism has been reported in many studies. Although future research could close some of the gaps that exist in terms of long-term outcomes, patients and providers should be optimistic for good outcomes with the treatment modalities currently available.

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Footnote

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