Considerations for Thyroidectomy as Treatment for Graves Disease

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ABSTRACT: Hyperthyroidism is a clinical state that results from abnormally elevated thyroid hormones. Thyroid gland affects many organ systems; therefore, patients usually present with multiple clinical manifestations that involve many organ systems such as the nervous, cardiovascular, muscular, and endocrine system as well as skin manifestations. Hyperthyroidism is most commonly caused by Graves disease, which is caused by autoantibodies to the thyrotropin receptor (TRAb). Other causes of hyperthyroidism include toxic multinodular goiter, toxic single adenoma, and thyroiditis. Diagnosis of hyperthyroidism can be established by measurement of thyroid-stimulating hormone (TSH), which will be suppressed with either elevated free T4 and/or T3 (overt hyperthyroidism) or normal free T3 and T4 (subclinical hyperthyroidism). Hyperthyroidism can be treated with antithyroid drugs (ATDs), radioactive iodine (RAI), or thyroidectomy. ATDs have a higher replacement rate when compared with RAI or thyroidectomy. Recent evidence has shown that thyroidectomy is a very effective, safe treatment modality for hyperthyroidism and can be performed as an outpatient procedure. This review article provides some of the most recent evidence on diagnosing and treating patients with hyperthyroidism.

KEYWORDS: Graves disease, thyroidectomy

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Introduction

The classic symptoms of palpitations, heat intolerance, tremor, and goiter have been identified in the medical literature throughout the ages as clinical manifestations of hyperthyroidism. The identification of the thyroid gland itself was established long before the description of hyperthyroidism, with references to goiters in the Chinese literature as early as 2700 BCE. The symptoms of hyperthyroidism were identified medically in the writings of Aristotle and Xenophon; however, the pathophysiology had not yet been identified. It was not until the 1800s CE that the disease triad of exophthalmos, palpitations, and goiter was identified by Irish physician Robert James Graves (1796-1853). Concurrently, Dr Carl Adolph Basedow (1799-1854) published similar findings in Germany. He described a triad akin to Graves, leading to a duality of naming for the disease in Europe for quite some time. Today, the name Graves disease has endured.[1]

A potential consequence of hyperthyroidism is thyrotoxicosis. This occurs in the state of physiologic excessive thyroid hormone. Normally, the thyroid gland produces triiodothyronine (T3) and thyroxine (T4) in response to thyroid-stimulating hormone (TSH) from the anterior pituitary gland. These hormones have physiologic effects in nearly every organ system such as cardiovascular, metabolism, growth, and gastrointestinal. Primary hyperthyroidism occurs when there is excess of T3 and T4 produced from the thyroid gland despite low TSH, ie, the thyroid is producing hormone despite a lack of normal stimulus. Secondary hyperthyroidism is defined by high levels of TSH which is in turn stimulating the thyroid to produce elevated levels of thyroid hormones.

Typically, in thyrotoxicosis, patients will have heat intolerance, palpitations, weight loss, tremor, anxiety, and hyperactive bowels. There are differing presentations of this condition in the young and in the elderly. Younger patients will have more overactive symptoms such as anxiousness, tremor, palpitations, and hyperactivity. An older patient in thyrotoxicosis tends to manifest with cardiovascular symptoms (tachycardia, atrial fibrillation) and weight loss.[2] In addition, in the elderly, the so-called "apathetic hyperthyroidism" can present with depression, lethargy, weight loss, and muscle wasting.[3]

A more serious condition, thyroid storm, occurs in the acute setting of severe thyrotoxicosis. Thyroid storm is a life-threatening complication that can be triggered by any acute stressor such as trauma, infection, or surgery. Clinical manifestations include exaggerated symptoms of hyperthyroidism: tachycardia that can be greater than 140 beats/min, persistent arrhythmia, marked hyperthermia, psychosis, or delirium. Prompt recognition and treatment with beta blockade, steroids, and propylthiouracil (PTU) are the keys to decreasing mortality.

Since the 2016 American Thyroid Association (ATA) guidelines were published, there have been some recent studies that were added to the literature that support and/or question the recommendations. Therefore, in addition to our comprehensive review of Graves disease and its management, this focuses more on the recently published evidence since the 2016 ATA guidelines were published.

Differentiating Cause of Primary Hyperthyroidism

Diagnosis of hyperthyroidism

The diagnosis of hyperthyroidism is based mainly on thyroid functioning tests. The best initial test is to measure a serum TSH level. Recently published evidence has shown that the use of TSH as a trigger to pursue further investigation of hyperthyroidism is still underused; therefore, many patients with hyperthyroidism remain undiagnosed.[4] If TSH is below 0.4 mU/L, serum T3 and T4 levels are then attained to determine severity. Radioactive iodine (RAI) uptake scans are used to distinguish Graves disease from toxic multinodular goiter (MNG) and toxic adenoma. In Graves disease, a diffuse uptake of RAI is shown. In contrast, toxic MNG demonstrates multiple foci of increased uptake. A toxic adenoma simply shows an area of increased uptake.[5] Additional laboratory testing can be performed if Graves disease is suspected, which includes thyrotropin receptor antibodies (TRAb), specific for Graves disease. This test is especially useful in patients who are pregnant or breastfeeding because RAI is potentially harmful to the fetus or infant. Classic symptoms of Graves disease include ophthalmopathy (eyelid retraction, proptosis, and periorbital edema), tachycardia, goiter, tremor, and warm/sweaty skin.[6]

Treatment of hyperthyroidism

Antithyroid drugs. Initial treatment of Graves disease focuses on symptomatic relief, with the ultimate goal being a euthyroid state. Beta blockers such as atenolol (25-50 mg/day) are used to control tachycardia, tremor, and palpitations. Other beta blockers such as propranolol and metoprolol can also be used. In patients with bronchospastic asthma, a B-1 selective agent can be used. If beta blockers cannot be tolerated, calcium channel blockers are next-line agents.[7] Treatment also includes decreasing the synthesis of thyroid hormones through antithyroid drugs (ATDs) or thionamides. Methimazole or PTU are used to achieve a euthyroid state via long-term management or until another treatment (radioiodine ablation or surgery) may be pursued.[8] Methimazole, the primary drug used in ATD therapy, works by inhibiting the synthesis of T3 and T4. It has a rapid onset and a relatively long duration of action compared with PTU, needing a once-daily dose of 5 to 40 mg. Methimazole has been found to be teratogenic and is thus contraindicated during the first trimester of pregnancy. Propylthiouracil is beneficial as it has not been found to be teratogenic and has an additional benefit of inhibiting peripheral conversion of T4 to the more potent T3. This added benefit makes PTU beneficial in acute treatment of thyroid storm; however, PTU is more associated with hepatotoxicity and is thus not first-line ATD treatment.[9] Class side effects of thionamides are allergic reactions (most common) and rarely agranulocytosis. Prior to initiation of treatment, a complete blood count (CBC) and liver panel should be drawn to establish a baseline for these labs. According to the 2016 ATA guidelines, clinical situations that favor medical treatment are patients with mild disease, small goiters, negative or low-titer TRAb, contraindication or high risk for surgery or RAI, patients with moderate to severe active Graves ophthalmopathy, and patients who need more rapid biochemical disease control.[7] However, ATDs have a higher failure rate of up to 48% in a recent study that included 720 patients followed for 3 years.[10]

RAI treatment. A definitive medical treatment for Graves disease is radioiodine ablation with an iodine-131 (131-I) dose of 150 to 200 mcCi/g. Ablation is then achieved over 12 to 18 weeks. The dose of radioiodine along this range is directly correlated with the cure rate of hyperthyroidism and incidence of hypothyroidism. Doses greater than 200 mcCi/g have not been associated with greater cure rates. Although RAI can produce high cure rates, there is still an 8% failure rate in the recent literature.[10] RAI can cause exacerbation of Graves disease; therefore, even in asymptomatic patients who are at an increased risk such as elderly patients and those with comorbidities, pretreatment with beta blockers and ATD should be considered. There is a greater risk of ophthalmopathy and hypothyroidism after the use of radioiodine ablation in Graves disease.[11] Radioablation is contraindicated in pregnancy and breastfeeding due to potential destruction of the fetus' or infant's thyroid and it is recommended for patients to delay a potential pregnancy for at least 6 months after treatment with 131-I. In addition, pregnancy test should be obtained within 48 hours prior to treatment. Radioactive iodine is recommended for individuals with an increased risk of surgery, previously operated or externally irradiated neck, and patients with contraindications to ATD use or failure to achieve euthyroidism during treatment with ATDs. A recent study also showed that 1.2% of patients undergoing RAI experienced radiation thyroiditis.[10] Long-term efficacy studies for use in children are yet to be established.

Surgical treatment. Thyroidectomy is the oldest and the preferred form of treatment for Graves disease. Despite being underused as a definitive treatment for hyperthyroidism according to a newly published large retrospective study,[4] thyroidectomy has been found to be as effective as ATDs and radioiodine in normalizing serum thyroid hormone levels within 6 weeks of therapy.[12] A meta-analysis that included 8 studies and a total of 1402 patients with hyperthyroidism has shown that thyroidectomy has the lowest relapse rate (10%) when compared with RAI (15%) and ATD (52%) as well as another meta-analysis which showed a 100% cure rate among patients who underwent total thyroidectomy.[10,13] In addition, thyroidectomy can be performed as an outpatient procedure in the hands of an experienced surgeon.[14] Indications for thyroidectomy include large goiters, goiters causing airway obstruction/dysphagia, moderate to severe ophthalmopathy (because radioiodine may worsen ophthalmopathy), pregnant or breastfeeding women, persistent hyperthyroidism after radioablation and

ATD therapy, or a nodule with abnormal cytology on fine needle aspiration (FNA).

Larger goiters are usually surgically resected because RAI alone may not be enough to sufficiently ablate the thyroid. If necessary, a postoperative dose of RAI is given to ablate any remaining thyroid tissue. Worsening of Graves ophthalmopathy by RAI is a well-documented risk associated with this treatment.[11,15] Similarly, surgery is commonly used for the treatment of patients with toxic MNG or toxic adenoma with obstructive symptoms, patients with coexisting hyperparathyroidism, and those who need definitive correction of hyperthyroidism. In pregnant and breastfeeding patients, PTU is the preferred treatment of Graves disease due to potential complications associated with surgery and PTU's relative safe use in pregnancy. If the patient is unable to tolerate PTU (or methimazole after the first trimester), then surgery is preferred. Finally, patients that have a coexisting suspicious or malignant thyroid nodule with Graves disease should opt for thyroidectomy. Although, according to Cantalamessa et al, most thyroid nodules in Graves disease are not associated with thyroid carcinoma, a total of 100 out of 315 patients in their study with Graves disease also had thyroid nodules 8 mm or larger. FNA of those nodules revealed carcinoma in only 1 patient. Thus, in Graves disease patients with normal cytology on FNA of thyroid nodule, thyroidectomy is not indicated.[16]

Preoperative Management

Once a diagnosis of hyperthyroidism is made, the first step to surgical management is symptomatic treatment and obtaining a euthyroid state. Many people believe that there is a risk of hemodynamic instability during anesthesia while in a hyperthryoid state and whenever possible; thyrotoxic patients should be rendered euthyroidic before undergoing surgery.[17] Beta blockers such as atenolol (25-50 mg/day) should be used up to and after surgery until thyroid function levels are within the normal limits. In patients who are unable to tolerate ATDs, beta blockers have been found to be more efficacious in controlling symptoms of hyperthyroidism in the preoperative setting.[18] Intravenous (IV) beta blockers can be used as needed. Antithyroid drug therapy is used up until the day of surgery. Although euthyroid is recommended in the current ATA guidelines, a few studies have found that there is no difference in outcomes for patients who are hyperthyroidic.[19–21] This can be important for people unable to achieve a euthyroid state or are unable to tolerate ATDs. According to the most recent ATA guidelines, preoperative potassium iodide (KI), saturated solution of potassium iodide (SSKI), or Lugol solution should be used in most patients with Graves.[7] This treatment has been shown to decrease thyroid blood flow, vascularity, and intraoperative blood loss.[22] Options include an SSKI 50 mg/drop 1 to 2 drops TID and should be initiated 7 to 10 days prior to surgery and discontinued the day of. An alternative pretreatment is Lugol solution (KI-iodine solution) 8 mg iodide/iodine per drop, 5 to 7 drops daily.[7] In addition, corticosteroid (betamethasone 0.5 mg every 6 hours) can be used for rapid preparation for emergent surgery.[23] There have also been other studies that have questioned this and show no change in outcomes when using these products.[24] Although this is the current recommendation, the exact benefit of use of these agents preoperatively on the outcome of surgery is still debated.

Calcium and vitamin D levels should be measured prior to surgery to establish a baseline level. If low, they may be replaced. Postoperative hypocalcemia can be avoided by pretreating with calcium carbonate 1 g TID for 3 weeks prior to the procedure.[25] Initial postoperative hypocalcemia is common due to shock to the parathyroid glands. Rarely does it develop into persistent hypoparathyroidism, unless the glands are removed with the thyroid. In patients with hypocalcemia and low vitamin D levels prior to surgery, calcitriol can be started in the preoperative or postoperative setting.[26]

Operative Considerations

Total thyroidectomy attempts to remove all of the thyroid tissue. Postoperatively, patients will be effectively hypothyroidic and become dependent on exogenous thyroid hormone. Subtotal thyroidectomy, while not as common as total thyroidectomy for surgical treatment of Graves disease, offers the benefit of potentially keeping the patient from lifelong thyroid hormone replacement therapy. According to the 2016 guidelines from the ATA for Diagnosis and Management of Hyperthyroidism, subtotal thyroidectomy that leaves 4 to 7 g of thyroid, in up to 60% of patients, allows them adequate thyroid function without the use of thyroid hormone replacement.[7] Similarly, to high/low-dose radioablation, total thyroidectomy versus subtotal thyroidectomy is a balance between risk of recurrence of hyperthyroidism and incidence of hypothyroidism. Total thyroidectomy is preferred to subtotal thyroidectomy to err on the side of hypothyroidism rather than risk recurrence.[27] In addition, in subtotal thyroidectomy, a second surgery may be needed to remove the remainder of the thyroid, which will be more difficult with the formation of scar tissue and distortion of tissue planes.[27] One randomized trial of total thyroidectomy vs subtotal thyroidectomy for the treatment of Graves disease by Barczynski et al followed 191 patients over a span of 5 years. It is found that patients undergoing total thyroidectomy had a recurrence of 0% as compared with a recurrence of 4.7% in patients undergoing subtotal thyroidectomy. Another consideration is the risk of hypoparathyroidism. The Barczynski et al's study found that 12.6% of total thyroidectomy patients had transient hypoparathyroidism and 0.5% had permanent hypoparathyroidism. In the subtotal thyroidectomy cohort, 6.8% had transient hypoparathyroidism and 0% had permanent hypoparathyroidism.[27] A more recent study of 215 068 patients comparing postoperative complications of thyroidectomies in Graves disease versus other indications for thyroidectomy shows a significantly higher rate of hypocalcemia, hematomas requiring reoperation, and longer hospital stays.

In this study, high-volume centers were indecently associated with a lower risk of postoperative complications. When compared with patients with MNG, they also found that Graves disease patients have higher odds of vocal cord paralysis, postoperative hypocalcemia, and hematoma requiring reoperation.[28]

A systematic review and meta-analysis of total vs subtotal thyroidectomy for Graves disease by Feroci et al[29] analyzed the incidences of recurrence of hyperthyroidism, transient hypoparathyroidism, permanent hypoparathyroidism, and recurrent laryngeal nerve injury. Whereas the odds ratio (OR) of transient and permanent hypoparathyroidism favors subtotal thyroidectomy, the OR of the recurrence of hyperthyroidism favors total thyroidectomy. Permanent recurrent laryngeal nerve injury was found to be equivalent between the 2 operations.[29]

Significant advances have been made in ligation device usage for thyroidectomy. Both LigaSure and Harmonic scalpel devices are used to achieve hemostasis and ligate. They are both superior to traditional knot tying techniques in reducing complications of hypoparathyroidism and transient recurrent laryngeal nerve injury.[30,31] In a 2010 study, Zarebczan et al compared the use of LigaSure and Harmonic scalpel in thyroid surgery. Of the 231 patients included in the retrospective chart review, 123 had total thyroidectomy. Although there was no statistically significant difference in complications of postoperative hypocalcemia, recurrent laryngeal nerve injury, or hematoma formation, the use of the Harmonic scalpel did reduce operative time by an average of 15 minutes compared with the LigaSure device in total thyroidectomy.[32] In addition, an improvement in patient outcome as well as a decrease in the length of stay and costs was observed when a high-volume surgeon performs thyroidectomy for Graves disease.[33,34]

Postoperative

At the time of surgery, ATD should be stopped and beta blockers should be tapered postoperatively. A few considerations are given postoperatively after thyroidectomy. Transient hypocalcemia is a common postoperative occurrence, present in 60% to 90% of patients undergoing total thyroidectomy.[26] Serum calcium and albumin levels should be measured in the postoperative setting. In addition, patients should be educated on the symptoms of persistent hypocalcemia. All patients should take 1000 mg calcium carbonate TID for 2 weeks until the levels of calcium and parathyroid hormone (PTH) are measured again. Parathyroid hormone is tested postoperatively after thyroidectomy to screen for transient and later permanent hypoparathyroidism.[35] This can occur as a result of shock to the parathyroid glands or unintentional resection. Thus, PTH levels are tested immediately in the postoperative setting. If the levels of intact parathyroid hormone (iPTH) are greater than or equal to 10 pg/mL, no supplemental calcitriol is needed. For iPTH values of 2 to 9 pg/mL, calcitriol 0.25 mcg BID is given. If the postoperative iPTH is less than 2 pg/mL, patients are prescribed 0.5 mcg calcitriol BID.[36]

In the euthyroid patient, thyroid hormone therapy should be initiated at a dose of 1.6 mcg/kg body weight daily. If the patient was hyperthyroidic leading up to surgery, T4 replacement should be delayed until thyroid hormone levels normalize. T4 has a half-life of about 1 week, so the initiation of hormone replacement should be estimated based on preoperative levels. Measurement of serum TSH should be obtained at 6 weeks postoperatively, and if TSH levels are high, the patient has reached a hypothyroid state and the thyroxine dose should be increased by 12 to 25 mcg/day.[37] Persistent hyperthyroidism is treated with RAI due to an increased risk of complications with subsequent surgeries.

Conclusions

The treatment of Graves disease should be tailored to the specific needs of each patient with the benefits and risks of each therapy explained in full. Surgery is preferred in the treatment of Graves disease in the cases discussed above: large obstructing goiter, pregnancy, breastfeeding, moderate to severe ophthalmopathy, persistent hyperthyroidism after radioablation and ATD therapy, inability to tolerate RAI or ATDs, or a nodule with abnormal cytology on FNA. Total thyroidectomy is, in most cases, a definitive treatment of hyperthyroidism due to Graves disease with the added benefits of rapid treatment, avoidance of RAI and ATD side effects, and an equally low risk of disease recurrence. Successful surgical treatment involves much more than pure surgical skill; it necessitates the appropriate preoperative and postoperative medical management of each aspect of the patient's disease.

Author Contributions

All authors have contributed to the writing of the paper.

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