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Is Hyperthyroidism Diagnosed and Treated Appropriately in the United States?

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Keywords

• Hyperthyroidism • Thyroid stimulating hormone • Underdiagnosis • Undertreatment • Thyroidectomy

Key points

- Recent studies suggest that hyperthyroidism is underdiagnosed and undertreated in the United States.
- Thyroid hormone has important effects on many organ systems and untreated hyperthyroidism can result in severe complications including cardiovascular disease and increased mortality.
- Hyperthyroidism should be suspected in patients with any clinical manifestations of the disease and screened for by obtaining a thyroid-stimulating hormone level.
- Hyperthyroidism can be readily treated through use of antithyroid drugs and more definitive therapies, such as radioactive iodine and total thyroidectomy.
- Diagnosis and treatment of hyperthyroidism warrant further study to understand the overall burden of cost to the US economy and health care system.

INTRODUCTION

Hyperthyroidism is a clinical condition that results from excessive levels of circulating thyroid hormone (thyroxine [T4] and tri-iodothyronine [T3], the active form). The prevalence of hyperthyroidism is 1.2% in the United States (0.5% overt and 0.7% subclinical) and 0.8% in Europe [1]. Worldwide, the

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most common etiologies are Graves' disease, followed by toxic multinodular goiter, and single toxic adenoma [2].

Although clinicians may suspect hyperthyroidism based on a wide variety of clinical signs and symptoms, the diagnosis is biochemical and made through demonstration of a suppressed thyroid-stimulating hormone (TSH) and/or elevated free T4 or T3. Further laboratory tests or imaging studies may be obtained for confirmation of the diagnosis and delineation of the etiology, such as the thyroid-stimulating immunoglobulin (TSI), thyrotropin receptor antibody (TRAb), and radiologic evaluation of the thyroid gland using radioactive iodine uptake (RAIU) scanning. Once the diagnosis of hyperthyroidism has been established, the key to definitive treatment lies in identification of the underlying cause of thyrotoxicosis. The 3 mainstays of therapy for hyperthyroidism are antithyroid drugs (ATDs), radioactive iodine (RAI), and surgery.

However, recent evidence suggests that hyperthyroidism may not be appropriately diagnosed and treated in the United States. In 1 study that identified all patients found to have a suppressed TSH at a large academic center, only 33% received further evaluation (including a repeat TSH), and 37% remained undiagnosed after further evaluation of their suppressed TSH [3]. Additionally, of those with an established diagnosis of hyperthyroidism, only 55% were referred for definitive therapy (34% to RAI and 21% to surgery) [3].

Therefore, this article highlights the most recent updates concerning the diagnosis and management of hyperthyroidism in the United States, and discusses potential implications of widespread underdiagnosis and undertreatment of hyperthyroidism.

SIGNIFICANCE

Disease impact on multiple organ systems

The thyroid gland affects nearly every organ system in the body, and owing to the potentially wide-reaching morbidities of undiagnosed and untreated disease, health care providers should maintain a higher level of suspicion for hyperthyroidism in patients presenting with any of its clinical manifestations. In 2016, the American Thyroid Association published guidelines recommending a comprehensive history and physical examination, including pulmonary, cardiac, and neuromuscular function evaluation, for all patients with suspected or known hyperthyroidism [2]. Hyperthyroidism symptoms are attributed to elevated thyroid hormone levels, and the wide range of clinical manifestations among these patients depends on the severity and duration of disease, patient age, comorbidities, and the underlying cause of hyperthyroidism. Some common clinical manifestations are independent of the underlying etiology, including sweating, heat intolerance, irritability, decreased concentration, anxiety, weight loss, and fatigue. Table 1 summarizes symptoms and signs of hyperthyroidism [4]. Other signs and symptoms are related to a specific etiology of hyperthyroidism, particularly Graves' disease, in which patients may present with ophthalmopathy and an infiltrative dermopathy where the skin is raised, hyperpigmented, and like an orange peel, particularly in the pretibial region.

Table 1
Symptoms and signs of hyperthyroidism

	Symptoms	Signs
Constitutional	Weight loss despite increased appetite; heat-related symptoms (heat intolerance, sweating, and polydipsia)	Weight loss
Neuromuscular	Tremor; nervousness; anxiety; fatigue; weakness; disturbed sleep; poor concentration	Tremor of the extremities; hyperactivity; hyperreflexia; pelvic and girdle muscle weakness
Cardiovascular	Palpitations	Tachycardia; systolic hypertension; irregular heartbeat (atrial fibrillation)
Pulmonary	Dyspnea, shortness of breath	Tachypnoea
Gastrointestinal	Hyperdefecation; nausea, vomiting	Abdominal tenderness
Skin	Increased perspiration	Warm and moist skin
Reproductive	—	Menstrual disturbances
Ocular (Graves' disease)	Diplopia; sense of irritation in the eyes; eyelid swelling; retroorbital pain or discomfort	Proptosis; eyelid retraction and lag; periorbital edema; conjunctival injection and chemosis; ophthalmoplegia

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Unique presentations of hyperthyroidism can be observed in particular patient age groups. In the pediatric population, hyperthyroidism has a negative effect on growth, development, and neuropsychiatric skills [5,6]. About 3% of children are affected by hyperthyroidism, with an incidence of 4.6 in 100,000 person-years in a population-based study conducted in France in 2015 [7]. Compared with adults, children presented more often with voice problems and difficulty concentrating, which may more directly affect their intellectual and communication skills during an important period of growth and development. Therefore, it is essential for the pediatric population with hyperthyroidism to be diagnosed and treated at an early stage. Additionally, behavioral problems, a short attention span, mood swings, and hyperactivity tend to be more common in hyperthyroid children when compared with adults [8].

By contrast, older patients (>60 years) with hyperthyroidism more often lack the classic symptoms of sympathetic hyperactivity (heat intolerance, tremor, sweating, and bowel hyperactivity) compared with younger patients. They present more frequently with weight loss, decreased appetite, shortness of breath, apathetic thyrotoxicosis (weakness and asthenia), and cardiac manifestations such as atrial fibrillation (AF) and tachycardia [9–12]. In a cross-sectional study of 3000 patients with hyperthyroidism, older patients had significantly fewer classical signs and symptoms of hyperthyroidism [10]. A national study in Denmark showed that 3% of 145,623 patients with new onset AF were found

to have hyperthyroidism, compared with 1% of the general population [13]. In addition, those who are older than 60 years were more likely to develop congestive heart failure and/or embolic stroke secondary to AF. Similarly, 17% patients with AF of unknown cause were found to have underlying undiagnosed hyperthyroidism [14]. In this group of patients, hyperthyroidism was found to be underdiagnosed and symptoms were sometimes misdiagnosed as depression [15].

Pregnant women with undiagnosed or untreated hyperthyroidism may present with pregnancy complications, such as spontaneous abortion, stillbirth, premature labor, low birth weight, preeclampsia, hypertension, or heart failure [16]. Last, patients may also present with thyroid storm, the most severe and life-threatening form of hyperthyroidism. Patients with untreated hyperthyroidism who subsequently have noncompliance with medications, infection, trauma, or any other form of stress are believed to be most at risk. Clinical manifestations of thyroid storm include cardiovascular complications such as severe tachycardia, AF, congestive heart failure, central nervous system alterations, gastrointestinal and hepatic disturbances, and death from cardiopulmonary and/or multiorgan failure [17]. Mortality from this rare syndrome was 10.7% to 25.0% in a case series that included 28 patients [17,18].

Physical examination of patients with hyperthyroidism should not be limited to just the neck. Evaluation of the neck should include inspection for distended neck veins as well as any asymmetry of the thyroid and palpation for enlargement, nodularity, fixation, and retrosternal extension. In some patients, a bruit may be auscultated over thyroid gland. Patients with hyperthyroidism will also express signs of a hyperactive sympathetic nervous system, including tremor, warm and sweaty hands, hyperreflexia, and occasionally muscle weakness. Cardiovascular examination often reveals tachycardia with elevated systolic blood pressure and hyperdynamic precordium, and patients with AF will have an irregularly irregular rhythm [11]. Patients may also demonstrate hyperactivity, rapid speech, anxiety, and a facial flushing. Finally, extrathyroidal features of Graves' disease such as ophthalmopathy (periorbital edema, lid lag and retraction, conjunctival redness and edema), dermopathy (as described), or pretibial myxedema may be prominent.

Laboratory and imaging evaluation

The first step in the evaluation for hyperthyroidism is measurement of serum TSH, because it has high sensitivity and specificity, and can also be used as a screening test [2]. Hyperthyroidism is routinely divided into 2 entities: overt and subclinical hyperthyroidism. In overt hyperthyroidism, TSH is usually suppressed to less than 0.04 mU/L (undetectable) with elevated T3 and/or T4. In subclinical hyperthyroidism, TSH is below the reference range, but T3 and T4 are within the normal range. Thus, an abnormally suppressed TSH should trigger further measurement of circulating thyroid hormones and total and free T4 and T3. Furthermore, in the majority of patients, the underlying etiology of hyperthyroidism is suspected based on the clinical

presentation, with the triad of exophthalmos, palpitations and goiter first described by Robert James Graves (1796–1853) continuing to be seen commonly today.

In relatively asymptomatic patients, however, the underlying etiology of hyperthyroidism may be unknown until after the diagnosis of hyperthyroidism is established. Such further evaluation can be accomplished by laboratory tests including measurement of TSI or TRAb, and imaging studies such as RAIU scan or measurement of thyroid blood flow on ultrasound. In the absence of a nodular goiter on physical examination, a diagnosis of Graves' disease can be confirmed by measurement of TSI or TRAb, which has sensitivity and specificity of 97% and 99%, respectively [2,19]. In the United States, measurement of TRAb has not been preferred in routine practice, and is often only considered in situations where RAIU is contraindicated. This is in contrast to the practice in Europe, Korea, and Japan, where TRAb is preferred over RAIU [20–23]. Additionally, TRAb has been shown to decrease overall costs by 47%, with a 46% faster time to diagnosis in an evidence-based economic model study in the United States [24].

Ultrasound examination has the ability to assess thyroid blood flow and evaluate the gland for abnormal nodules that would warrant further testing such as fine needle aspiration biopsy. The 2016 American Thyroid Association guidelines recommend RAIU if the clinical presentation suggests toxic multinodular goiter or toxic adenoma, but thyroid Doppler ultrasound examination for pregnant and breastfeeding women or other patients for whom RAIU is contraindicated [2]. For Graves' disease, one cost-effectiveness study comparing ultrasound examination with RAIU found ultrasound examination to be more cost-effective and sensitive for diagnosis compared with RAIU, 97.2% versus 95.2%, respectively [25]. Additionally, ultrasound examination has the advantages of being inexpensive, noninvasive, and patients are not exposed to any ionizing radiation. Furthermore, the accuracy of ultrasound examination can be improved by using color flow Doppler techniques. Thyroid gland vascularity, especially flow through the inferior thyroid artery, can be diagnostic, with high flow consistent with Graves' disease and low flow more indicative of destructive thyroiditis [26–28]. Additionally, change in echogenicity across serial ultrasound examinations has been shown to predict both remission after initiation of ATDs and to identify patients at high risk for recurrence after ATD withdrawal. Ultrasound examination can also identify and characterize incidental thyroid nodules, which have been reported in 16% of Graves' disease patients in 1 series [25].

RAI I^{131} uptake is commonly used in the United States to identify the underlying etiology of hyperthyroidism. Hyperactive thyroid tissue will trap and organify the radiolabeled iodine, and this can be measured by a gamma camera after an interval of 24 hours. Pregnancy and breastfeeding are absolute contraindications to RAIU scanning. When obtained, RAIU scans show increased diffusely homogenous uptake in Graves' disease, asymmetric irregular uptake in toxic multinodular goiter, and an area of focally increased uptake in toxic

adenoma. In contrast, normal to low RAI uptake will be observed in destructive conditions such as subacute, viral, and postpartum thyroiditis, and with exogenous thyroid hormone administration. Although RAIU is still considered by some to be a useful tool for calculating the dose of iodine for those opting to receive RAI therapy as definitive treatment, this is discouraged by the European guidelines for patients receiving RAI owing to its poor prognostic ability, higher cost, patient inconvenience, and radioactive isotope exposure [20,29,30]. Owing to its low sensitivity in detecting thyroid nodules as well as higher cost compared with ultrasound examination, the usefulness of RAIU scans for patients with hyperthyroidism is limited and can be reserved for selected cases where the diagnosis cannot be clearly established by laboratory evaluation and ultrasound examination [20,25,31].

Treatment of hyperthyroidism

Antithyroid drugs

ATDs may be used to achieve a euthyroid state for remission of thyrotoxicosis or before a more definitive treatment such as RAI or surgery. The 2 major ATDs used in the United States are methimazole (MMI) and propylthiouracil (PTU). Both drugs are absorbed by the thyroid and bind to thyroid peroxidase, preventing the coupling of iodide to the tyrosyl residues of thyroglobulin, inhibiting the synthesis of T3 and T4. PTU additionally acts on peripheral tissues to inhibit tetraiodothyronine 5′ deiodinase from converting T4 to T3. The use of PTU in the first trimester of pregnancy is preferred over MMI as protein binding decreases its ability to cross the placenta. Both PTU and MMI have been associated with adverse effects, including rash, hepatotoxicity, and agranulocytosis, in up to 13% of patients in 1 study [32]. Of these patients, those treated with MMI experienced adverse effects more often than those taking PTU (14.9% vs 6.9%; odds ratio, 2.3; 95% confidence interval [CI], 1.80–3.06), however, hepatotoxicity was more common with PTU administration (2.7% vs <1.0%) [32]. Agranulocytosis was similarly rare with both medications, occurring in less than 1% of patients on ATDs [32]. Therefore, before the initiation of ATDs, patients should have a complete blood count and liver function tests, and receive education about the symptoms of allergic reaction, hepatotoxicity, and agranulocytosis. They should be instructed to stop these medications and call their prescribing physician if they have any symptomatology. When evaluating the use of ATDs in Graves' disease, the rate of relapse for both high- and low-dose regimens are 51% and 54%, respectively [33]. The optimal duration of treatment of Graves' disease with ATD is 12 to 18 months; use beyond 18 months has not demonstrated benefit [33]. Regarding cost, the use of ATDs for more than 12 months has been shown to have a higher cost of therapy when compared with patients undergoing RAI, without a difference in achieving a euthyroid state [34].

Radioactive iodine ablation

The oral administration of I^{131} results in uptake of radioiodine by thyroid follicular cells, which results in the release of β-ray emission and subsequent

follicular cell destruction. Although this is the most common method of definitive treatment for hyperthyroidism in the United States, it is suboptimal for patients needing rapid control of symptoms or those with organ dysfunction secondary to hyperthyroidism, as the treatment effect takes 6 to 8 weeks on average, and can be as long as 6 months. After an initial dose of RAI, 86% of patients achieve a euthyroid or hypothyroid state [35]. An additional dose of RAI may be given to patients that have persistent hyperthyroidism after 4 to 6 months. A second dose is more likely necessary in patients who have received lower doses of RAI (185 MBq) when compared with patients receiving higher doses (370 MBq) [36].

RAI is contraindicated in patients who are pregnant, breastfeeding, or plan to become pregnant within 6 months after therapy, because it crosses the placenta and may be concentrated within the fetal thyroid at 10 to 12 months of gestation [37]. Owing to concerns for thyroid cancer later in life as well as precipitation of other secondary neoplasms, RAI is relatively contraindicated in children and those in close contact with children. Patients who undergo RAI for multinodular goiter have been shown to have increased risk of thyroid cancer mortality [38]. RAI has also been linked to an increased incidence of cancers in organs that concentrate I^{131} (salivary glands, kidneys, bladder), as well as those in the breast, digestive, and respiratory tracts [39–42]. Severe ophthalmopathy may be worsened with the use of RAI in approximately 15% of patients; therefore, it is a relative contraindication. Tallstedt and colleagues [43] performed a randomized, controlled trial of patients receiving RAI for Graves' disease compared with patients receiving MMI for 18 months or subtotal thyroidectomy. They demonstrated that patients who underwent RAI had statistically significant worsening of their ophthalmopathy compared with patients treated with MMI or surgery (33% vs 10% and 13%, respectively; $P = .02$) [44]. When comparing 2793 patients undergoing RAI with age- and gender-matched controls, Metso and colleagues [45] found that there was an increase in all-cause mortality (rate ratio, 1.12; 95% CI, 1.03–1.20). This increased mortality rate was found to be due to cerebrovascular disease and cancer. Additionally, the risk of mortality increased with rising RAI dose in patients with nodular thyroid disease, but not Graves' disease [45]. Franklyn and colleagues [46] found significantly increased mortality in 7209 patients treated with RAI for hyperthyroidism owing to all causes (standardized mortality ratio [SMR], 1.1; 95% CI, 1.1–1.2; $P < .001$), cardiovascular disease (SMR, 1.2; 95% CI, 1.2–1.3), and cerebrovascular disease (SMR, 1.4; 95% CI, 1.2–1.5), and fracture (SMR, 2.9; 95% CI, 2.0–3.9) when compared with population age-matched controls. Mortality increase in this study was the most apparent in the year after RAI administration.

Surgery

Surgery is the preferred treatment for thyrotoxicosis in patients with compressive symptoms, thyroid nodule(s) concerning for malignancy, contraindication to RAI, children, severe Graves' orbitopathy, and patient preference. Owing to

the risk of thyroid storm, patients should be relatively euthyroid before undergoing surgery. This may be achieved with ATDs or inorganic iodide. Symptomatic control of thyrotoxicosis may be achieved with the use of beta-blockade while ATDs take effect, which may take several weeks. Inorganic iodide may be administered as oral saturated potassium iodide (Lugol's solution), or intravenous sodium iodide. Iodide acts through the Wolff-Chaikoff effect, which inhibits the organification of iodine in the thyroid, inhibits the production of thyroid hormone, and prevents the release of thyroid hormone. The mainstay of surgical treatment for hyperthyroidism is total thyroidectomy, and is indicated in toxic multinodular goiter and amiodarone-induced thyrotoxicosis poorly managed with medication. For patients with Graves' disease, total thyroidectomy is also the treatment of choice owing to risk of recurrence, which has been shown to be 7.9% to 23.8% with subtotal thyroidectomy [47–49]. The risk of recurrence of Graves' disease after surgery is nearly 0% for total thyroidectomy [49]. The only indication for subtotal thyroidectomy in patients with hyperthyroidism is that owing to a solitary toxic nodule, when the contralateral thyroid lobe is without abnormality. Thyroidectomy, when performed by a surgeon who performs 25 or more thyroidectomies a year, carries a low risk of complications [50,51]. The risk of permanent hypoparathyroidism is less than 2%, permanent recurrent laryngeal nerve injury is less than 1%, and need for reoperation owing to bleeding 0.3% to 0.7% [52,53]. These risks are slightly increased in patients with Graves' disease, with rates of permanent hypoparathyroidism being 1.8%, permanent recurrent laryngeal nerve injury being 1.8%, and immediate postoperative bleeding being 1.0% [54]. More recently, evidence has shown that thyroidectomy can be safe and effective, even if it is done in an outpatient setting for patients with Grave's disease [55].

Treatment of thyroid storm

Treatment of thyroid storm requires supportive therapy, reduction of thyroid hormone levels, and treatment of the underlying cause, including the definitive management of hyperthyroidism. Reduction of thyroid hormone should be achieved with PTU, because it not only blocks the synthesis of thyroid hormone, but also the peripheral conversion of T4 to T3. Inorganic iodide may be used to stun the thyroid and prevent further production and release of thyroid hormone. The systemic effects of thyroid storm should additionally be managed with the administration of beta-blocker (propranolol), steroids, intravenous fluids, and external cooling, among other potential therapies. Although these patients are not ideal operative candidates, they often require surgery to achieve immediate and definitive management of their thyrotoxicosis.

DISCUSSION (PRESENT RELEVANCE AND FUTURE AVENUES)

Underdiagnosis of hyperthyroidism

In the United States, despite widespread availability of thyroid function laboratory assessment, as well as an increasing number of people with access to health

care, a large number of patients with both overt and subclinical hyperthyroidism remain undiagnosed [3]. A recently published, large, retrospective study of 3336 patients with suppressed TSH revealed that 67% did not undergo further evaluation for their suppressed TSH (T3, T4, thyroid peroxidase antibodies, TSI, or RAIU) and hyperthyroidism remained undiagnosed in 37% of patients who had the appropriate workup [3]. Contrary to the conventional approach, thyroid peroxidase antibody evaluation was more frequently obtained (51%) in this study compared with T3 (20%) and T4 (22%). Interestingly, patient age group, race, and presentation symptoms were associated with an increased likelihood of hyperthyroidism diagnosis. Asban and colleagues [3] found that patients who are younger, African American, present with ophthalmopathy or weight loss, have no medical comorbidities, have private commercial insurance, lower TSH, and are in the outpatient setting were more likely to be recommended for further workup and evaluation among all patients with suppressed TSH. The authors attributed these findings to both a failure of the system to recognize a suppressed TSH as the first clinical finding for hyperthyroidism and alert health care providers, as well as to a knowledge gap among health care providers in understanding the gravity of untreated hyperthyroidism and the need for urgency in further work up and potential treatment [56,57]. To mitigate the system factors, some institutions have implemented algorithms to trigger an automatic serum free T3 and T4 in cases with a suppressed TSH [58]. Although this approach has a significant upfront cost, it likely pales in comparison to the costs of undiagnosed hyperthyroidism and its subsequent complications, especially cardiovascular disease, the leading cause of mortality in hyperthyroid patients [59]. Ongoing research into the prevalence and cost effectiveness of hyperthyroidism diagnostic algorithms is needed.

Undertreatment of hyperthyroidism

Sundaresh and colleagues [32] performed a metaanalysis of 8 studies including 1402 patients undergoing treatment for Graves' hyperthyroidism. Their findings demonstrated that patients treated with ATDs (52%) had higher relapse rates than RAI (15%) and surgery (10%). When comparing treatment modalities for Graves' disease across multiple studies, patients treated surgically consistently have the lowest recurrence rates. Torring and colleagues [60] performed a randomized, controlled trial of 179 patients undergoing treatment for Graves' disease where younger patients (18–34 years) were randomized to treatment with ATDs for 18 months versus subtotal thyroidectomy, and older patients (35–55 years) were randomized to receive ATDs, RAI, or subtotal thyroidectomy. Their results demonstrated relapse of 42% and 34% in both young and older medically treated groups, respectively, and those treated with RAI had a relapse rate of 21%. Patients in the surgical treatment group had the lowest rate of relapse, 3% and 8% for young and older patients, respectively. Palit and colleagues [48] performed a metaanalysis of 35 studies including 538 patients who underwent total thyroidectomy for Graves' disease, and their

results demonstrated that all patients (100%) achieved hypothyroidism, with low rates of permanent complications: 0.9% recurrent laryngeal nerve injury and 1.6% hypoparathyroidism.

Despite the demonstrated safety and efficacy of total thyroidectomy for the treatment of hyperthyroidism, patients in the United States are most often treated with RAI. At our institution, only 21% of patients were referred to a surgeon for thyroidectomy despite evidence demonstrating lower relapse rates with surgical intervention when compared with alternative treatments [3]. In the hands of an experienced surgeon, the risks of thyroidectomy for Graves' disease are low (permanent hypoparathyroidism, <2%; permanent recurrent laryngeal nerve injury, 1.8%; and immediate postoperative bleeding, 1%) [54], particularly when compared with the 13% rate of adverse effects from ATD administration and complications of RAI, which include worsening orbitopathy, increased mortality rates, and increased risk of thyroid cancers and secondary malignancies. Further evaluation of the current treatment practices in the United States should be conducted to determine if hyperthyroidism patients broadly are receiving the most efficacious and cost-effective care, which will likely include surgical therapy for a larger population than that identified in current studies.

SUMMARY

To date, hyperthyroidism remains largely underdiagnosed and undertreated in the United States. Although thyroidectomy is the most effective definitive treatment modality, it is still underused despite the increasing evidence for its safety, efficacy, and long-term cost reduction. Underdiagnosis and undertreatment of hyperthyroidism could harbor a significant impact on health care costs in the United States, as well as directly impacting the outcomes of patients who suffer from the disease, given the vast effect of thyroid hormone on multiple tissues and organ systems. Therefore, future research should be directed toward identifying the most effective approaches to early detection of disease both by educating health care providers to have a high index of suspicion to further investigate patients with disease manifestations, and the institution of systems to automatically evaluate further all patients with a suppressed TSH. Finally, more definitive and effective treatment options, including total thyroidectomy, should be adopted by endocrinologists as well as primary care providers.

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