



# Thyrotoxicosis: Diagnosis and Management

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## Abstract

Thyrotoxicosis is the clinical manifestation of excess thyroid hormone action at the tissue level due to inappropriately high circulating thyroid hormone concentrations. Hyperthyroidism, a subset of thyrotoxicosis, refers specifically to excess thyroid hormone synthesis and secretion by the thyroid gland. We performed a review of the literature on these topics utilizing published data in PubMed and MEDLINE. In this review, we discuss the more common etiologies of thyrotoxicosis, focusing on the current approach to diagnosis and management, new trends in those directions, and potential upcoming changes in the field.

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Thyrotoxicosis is the clinical manifestation of a group of disorders characterized by the presence of excess thyroid hormone action at the tissue level and is the consequence of inappropriately high thyroid hormone concentrations.<sup>1</sup> Hyperthyroidism, a subset of thyrotoxicosis, refers specifically to excess thyroid hormone synthesis and secretion by the thyroid gland. The prevalence of hyperthyroidism is 1.3% in the United States.<sup>2</sup> It occurs more commonly in women compared with men (2% vs 0.2%),<sup>3</sup> and the incidence increases with age, iodine deficiency, and race (higher in whites compared with Hispanics and African Americans).<sup>4</sup> We conducted a comprehensive search of PubMed and MEDLINE for English language articles using the terms *hyperthyroidism* and *thyrotoxicosis* with no limits on date. The current review is based on the most recent and highest-quality evidence available.

## ETIOLOGY

Thyrotoxicosis results from inappropriate activation at any level of the hypothalamic-pituitary-thyroid axis with increased thyroid hormone production from thyroid follicles or from release or ingestion of preformed thyroid hormone (Table 1). In iodine-sufficient areas, the most common cause of noniatrogenic thyrotoxicosis is Graves disease (GD), which accounts for 80% of cases,<sup>5</sup> followed by nodular thyroid disease and thyroiditis. The frequency

of these etiologies, however, varies with the level of iodine intake (nodular thyroid disease accounts for as much as 50% of cases in iodine-deficient regions),<sup>5</sup> the age of the population (toxic nodular goiter is more common in the elderly),<sup>6</sup> and with the region studied (frequency of painless thyroiditis was 0.5% in Denmark vs 22% in Wisconsin<sup>7,8</sup>).

## THYROTOXICOSIS WITH HYPERTHYROIDISM

### Graves Disease

**History.** Caleb Parry (1755-1822), a physician and farmer from Bath, England, described 2 cases of goiter and palpitations.<sup>9</sup> His case records were published posthumously in 1825 by his son.<sup>10</sup> Robert J. Graves (1796-1853), chief physician at the Meath Hospital in Dublin, Ireland, described 3 cases of women with goiter and palpitations in 1824-1825. In 1835, 4 cases were reported (the fourth case had exophthalmos and was added by his colleague William Stokes), and in 1843 the entity of “GD” was described in his book.<sup>11</sup> In 1840, Karl von (1799-1854), a German physician, also reported a case with palpitations, goiter, and exophthalmos (Merseburg triad).<sup>12</sup> Graves overlooked Parry’s reports, and Basedow overlooked Graves’. The disease, therefore, has been referred to as Parry disease, GD, and Basedow syndrome, depending on the geographic and cultural area involved. In 1862, the eponymous honor was given to

**Epidemiology and Pathogenesis.** Graves disease is the most common cause of hyperthyroidism. It has an annual incidence of 20 to 50 cases per 100,000 persons and a lifetime risk of 3% in women and 0.5% in men.<sup>13</sup> The

of GD is strongly influenced by . A family history of thyroid dysfunction has been found in approximately half of individuals with GD.<sup>14</sup> Twin concordance studies suggest that up to 80% of risk is due to genetic factors.<sup>15</sup> Many of the genes associated with an increased risk of

( arthritis, type mellitus, and ).<sup>16</sup> Genes conferring an increased risk for GD include *HLA-DRB1\*03* (for expansion of gene symbols, use search tool at [www.genenames.org](http://www.genenames.org)), *HLA-DRB1\*08*, and (TSH), the protein tyrosine phosphatase nonreceptor type 22 (*PTPN22*), cytotoxic T-lymphocyte antigen 4 (*CTLA4*), CD25, and CD40.<sup>17,18</sup> Environmental factors such as cigarette smoking, dietary iodine, infection with *Yersinia enterocolitica* (due to molecular mimicry with the TSH receptor), and stress also play a role.<sup>19,20</sup>

**Diagnosis.** Symptoms and signs of GD are usually due to the underlying or . The most common manifestations are , tremor, and . Atrial is seen in of individuals older than 60 years, whereas a palpable is more common in those than years.<sup>19</sup> Clinically important ( ) occurs in of patients with GD; however, sub-clinical eye involvement with extraocular muscle enlargement can be seen radiographically in up to 70% of patients.<sup>21</sup> Eye muscle , and ocular pain are the of GO.<sup>22</sup> Thyroid is uncommon (occurring in only 1%-4% of individuals with GD),

ARTICLE HIGHLIGHTS

- Thyrotropin receptor antibody assay, radioactive iodine uptake and scan, and thyroid ultrasonography with color flow Doppler remain important tools for determining the cause of thyrotoxicosis.
- There is a changing trend in Graves disease therapy with decreasing preference for radioactive iodine therapy and increasing use of antithyroid drugs, including the use of long-term antithyroid drug therapy, which is deemed safe and effective.
- Biotin use is a potential risk factor for spurious diagnosis of thyrotoxicosis.
- New anticancer drugs—tyrosine kinase inhibitors and immune checkpoint inhibitors—are causing thyroiditis, and thyroid function monitoring should be considered in patients who take these drugs.
- Immunomodulatory therapy is being tested in clinical trials to directly address the pathogenesis of Graves disease.

is pathognomonic for thyroid autoimmunity, and is almost always associated with GO. Thyroid acropachy is even more rare, occurring in only 20% of patients with thyroid dermatopathy.<sup>23</sup>

Graves disease should be suspected in the presence of clinical findings of with biochemical ( serum and thyroxine [ ] or triiodothyronine [ ]). If pathognomonic signs are present (diffuse goiter with , , or ), no further testing is required to establish the diagnosis. In the absence of these signs, measurement of (TRAbs) (97% sensitivity and 98%-99% specificity for GD)<sup>24</sup> can be helpful, especially in the setting of a nodular goiter.<sup>25</sup>

(RAIU) with diffuse distribution on the scan can also the diagnosis and distinguishes GD from other causes of thyrotoxicosis (Figure 1). More recently, color flow Doppler sonography (CFDS) with thyroid ultrasound has been employed with good accuracy for GD diagnosis as well (sensitivity of 87% and specificity of 100%).<sup>26</sup>

TABLE 1. Causes of Thyrotoxicosis

Etiology	Mechanism
Thyrotoxicosis with hyperthyroidism (increased thyroid hormone synthesis)	
Thyroidal origin	
Graves disease	TSHR-stimulating antibody
Toxic multinodular goiter	Activating TSHR of G proteins
Solitary toxic adenoma	Focal thyroid autonomy
TSH-secreting pituitary adenoma	Autonomous TSH secretion
Neonatal Graves disease	Thyroid-stimulating immunoglobulins
Congenital hyperthyroidism	Activating mutations in TSHR
Familial gestational hyperthyroidism	Activating mutations in TSHR
Pituitary resistance to thyroid hormone	Mutated thyroid hormone receptor $\beta$
Choriocarcinoma	Human chorionic gonadotropin secretion
Hyperemesis gravidarum	Human chorionic gonadotropin secretion
Iodine, iodine-containing drugs (eg, amiodarone), radiographic contrast agents	Jod-Basedow phenomenon
Extrathyroidal origin	
Struma ovarii	Thyroid hormone production by dermoid tumor of ovary
Metastatic follicular thyroid cancer	Extrathyroidal foci of thyroid hormone production
Thyrotoxicosis without hyperthyroidism (increased availability of preformed thyroid hormone)	
Thyroidal origin	
Silent (painless) and postpartum thyroiditis	Release of stored thyroid hormone
Subacute thyroiditis	Postviral infection
Drug-induced thyroiditis (eg, amiodarone-AIT2, interferon- $\alpha$ , lithium, PD-1 inhibitors, TKI)	Destruction of thyroid follicles
Acute infectious thyroiditis	Bacterial or fungal infection
Radiation thyroiditis	Thyroid cellular destruction and release of stored thyroid hormone
Thyroid adenoma infarction	Release of stored thyroid hormone
Extrathyroidal origin	
Exogenous thyroid hormone	Ingestion of thyroid hormone

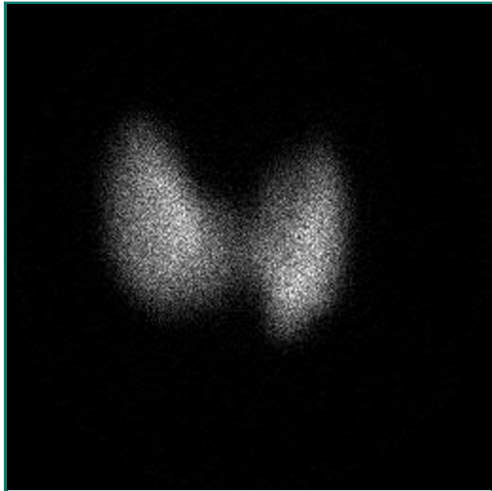
AIT2 = amiodarone-induced thyroiditis type 2; PD-1 = programmed cell death 1; TKI = tyrosine kinase inhibitor; TSH = thyrotropin; TSHR = TSH receptor.

**Treatment.** The management of GD is 2-fold: symptom control and treatment of the underlying hyperthyroidism. Most of the symptoms are due to overstimulation of  $\beta$ -adrenergic receptors.  $\beta$ -Blockade, therefore, is the mainstay of symptom control. Nonselective propranolol offers the additional benefit of decreasing the peripheral conversion of  $T_4$  to  $T_3$ .<sup>27</sup> In a thyroid storm, glucocorticoids are also used for this purpose.<sup>28</sup>

Radioactive iodine ablation, antithyroid drugs (ATDs), and thyroidectomy are the mainstay treatment options for the underlying hyperthyroidism (Table 2). Radioactive iodine has been the preferred first-line approach in the United States (unlike Europe, where

ATDs are favored)<sup>34</sup>; however, its use has been decreasing.<sup>35,36</sup> Interestingly, quality of life after treatment is no different regardless of treatment modality.<sup>32</sup>

Radioactive iodine I 131 is incorporated into thyroid tissue through the sodium-iodine symporter. The expression of the sodium-iodine symporter gene is dependent on TSH receptor activation. This occurs diffusely in GD, and therefore, RAI I 131 is incorporated into the entire thyroid gland. Tissue necrosis ensues over the subsequent 6 to 18 weeks, resulting in hypothyroidism in 80% to 90% patients after a single dose.<sup>33</sup> As with many radiation-based therapies, a negative pregnancy test result is required before RAI treatment for all women of childbearing potential.



**FIGURE 1.** Radioactive iodine I 123 uptake image showing diffuse thyroid uptake in a patient with Graves disease.

Antithyroid drugs inhibit thyroid hormone synthesis by disrupting thyroid peroxidase (TPO) iodination of tyrosine residues on thyroglobulin—a critical step in the formation of T<sub>3</sub> and T<sub>4</sub>. Propylthiouracil (PTU) and methimazole are both available in the United States, with the former providing an additional benefit of decreasing T<sub>4</sub> to T<sub>3</sub> conversion. However, methimazole is the preferred drug in the United States given the concerns about severe hepatotoxicity associated with PTU.<sup>37</sup> Carbimazole, a prodrug to methimazole, is used in the British Commonwealth with similar effects to methimazole. For most patients, ATDs are utilized alone with the dose titrated to achieve euthyroidism. It is worth noting that in some parts of the world outside the United States, an alternative approach called “block and replace” is also employed in patients who have rapid fluctuations between hypothyroidism and hyperthyroidism: ATDs are used at a fixed dose and combined with levothyroxine (LT<sub>4</sub>) to achieve euthyroidism. This regimen might be associated with less frequent clinic visits and laboratory testing.<sup>38</sup>

Initial dosing of methimazole is selected on the basis of the clinical and biochemical severity of thyrotoxicosis. Mild hyperthyroidism (typically with a free T<sub>4</sub> level 1-1.5 times the upper limit of normal) is treated

with low-dose methimazole (5-10 mg daily), moderate hyperthyroidism (frequently with a free T<sub>4</sub> level 1.5-2 times the upper limit of normal) can be treated starting with 10 to 20 mg of methimazole, and severe hyperthyroidism (free T<sub>4</sub> level  $\geq$ 2-3 times the upper limit of normal) is treated with high-dose methimazole (20-40 mg daily) in divided doses.<sup>39</sup>

Antithyroid drugs are typically given for 18 months and then withdrawn to determine remission, which is defined as no recurrence of GD after 12 months without treatment. The remission rate with ATDs is 30% to 50% in the United States<sup>40,41</sup> and 50% to 60% in Europe.<sup>42</sup> The following factors decrease the likelihood of remission: male sex, age less than 40 years, previous recurrence of GD, cigarette smoking, large goiter, orbitopathy, high ratio of free T<sub>3</sub> to free T<sub>4</sub>, high titers of TRAb at diagnosis, and the end of the course of ATDs.<sup>43-46</sup>

Adverse reactions occur in 13% of patients taking ATDs. Cutaneous reactions are more common with methimazole; however, hepatotoxicity is more common with PTU.<sup>29,47</sup> Risk of hepatitis is ATD dose dependent, increasing considerably with higher doses of both PTU and methimazole (low-dose PTU vs high-dose PTU hazard ratio, 0.39; high-dose methimazole hazard ratio of 5.08 vs low-dose methimazole hazard ratio of 1.15 compared with PTU).<sup>48</sup> Long-term use of ATDs has been reported over the years<sup>49</sup> and is usually favored in patients with GO. This trend has increased in recent years, and there is suggestion of benefits (ie, weight stability, less frequent dysthyroidism, better GO outcome) from maintaining endogenous thyroid hormone production with ATDs as opposed to achieving euthyroidism with LT<sub>4</sub> after RAI.<sup>50</sup> Reassuringly, the adverse effects associated with ATDs are very unlikely to develop after the first 3 to 6 months of therapy. Thus, the incidence of hepatotoxicity decreases from 30 per 1000 patient-years at 30 days on methimazole to less than 1 per 1000 patient-years after 180 days on methimazole,<sup>48,49,51,52</sup> and there has been only one case of serious adverse effects that have occurred in adults after 12 months of ATD

TABLE 2. Treatment of Graves Disease<sup>a</sup>

Treatment	Mechanism	Dosing	Remission rate	Adverse effects	Pregnancy
ATDs ● MMI ● PTU <sup>b</sup>	Block TPO action	Initial dose proportional to degree of elevation of thyroid hormones, symptoms, and goiter size	30%-60%	Dependent on dose and duration of therapy (total, 13%) <sup>29</sup> ● Rash ● Elevated liver enzymes ● Agranulocytosis (0.3%) ● Vasculitis <sup>c</sup> (<0.1%) <sup>30</sup>	<u>MMI</u> ↑ Risk of congenital abnormalities; recommended in 2nd and 3rd trimester <sup>31</sup> <u>PTU</u> Lower teratogenic risk but ↑ risk of hepatotoxicity; recommended in 1st trimester <u>All ATDs</u> ↑ Risk of fetal hypothyroidism
Radioactive iodine I 131	Radiation-induced thyroid follicular cell necrosis	Fixed or calculated dose based on goiter size and uptake <sup>19</sup>	80%-90% <sup>32,33</sup>	Worsening thyrotoxicosis, radiation thyroiditis, worsening orbitopathy	Contraindicated in pregnancy and lactation
Thyroid surgery	Surgical removal of visible thyroid tissue	Total thyroid-ectomy	100%	Hypoparathyroidism, laryngeal nerve injury	Can be performed in 2nd trimester <sup>1</sup>

<sup>a</sup>ATDs = antithyroid drugs; MMI = methimazole; PTU = propylthiouracil; TPO = thyroid peroxidase; T<sub>3</sub> = triiodothyronine; T<sub>4</sub> = thyroxine; ↑ = increased.

<sup>b</sup>Blocks TPO and peripheral T<sub>4</sub> to T<sub>3</sub> conversion.

<sup>c</sup>Reported with PTU.

therapy, a case of vasculitis that developed after the use of PTU for 6 years.<sup>51</sup>

If thyroidectomy is chosen, patients should be pretreated with ATDs and  $\beta$ -blockers to induce euthyroidism before surgery.<sup>53</sup> Iodine solutions (saturated solution of potassium iodide or Lugol solution) are taken for 10 days preoperatively to help normalize thyroid hormone levels, decrease thyroid vascularity, and minimize surgical blood loss. In addition, calcium and vitamin D levels should be assessed and repleted before surgery to prevent development of symptomatic postoperative hypocalcemia.<sup>54</sup> The operation should be performed by a high-volume thyroid surgeon (>25 thyroidectomies per year), which has been associated with improved patient outcomes.<sup>55</sup>

An individualized approach taking into account patient preference, clinical factors, availability of and expertise with the treatment options, and cost should be considered before deciding on the first treatment approach. For example, in a young woman who desires future pregnancy, RAI and surgery are favored because of the increased incidence of congenital malformations seen with ATDs during pregnancy.<sup>31,56</sup> However,

ATDs are favored in patients with a high likelihood of remission or with severe GO. Thyroidectomy is preferred when there are symptoms of compression from large goiters, suspicious nodules, or moderate to severe and active orbitopathy in patients who cannot tolerate ATDs.<sup>1</sup>

Follow-up depends on the treatment modality chosen. At 6 to 10 weeks after RAI, free T<sub>4</sub> and total T<sub>3</sub> should be assessed and then monitored every 2 to 4 weeks thereafter until there is evidence of progression toward hypothyroidism, when LT<sub>4</sub> therapy should be initiated.<sup>1</sup> If an ATD is chosen, measurement of free T<sub>4</sub> and total T<sub>3</sub> should be performed every 2 to 6 weeks until euthyroidism is achieved. The dose should be decreased on the basis of declining free T<sub>4</sub> and T<sub>3</sub> levels and achievement of euthyroidism. Once the lowest dose to maintain euthyroidism is apparent, this dose should be continued with laboratory assessment every 2 to 3 months or every 6 months if long-term ATD therapy has been chosen. Currently, there is insufficient evidence to support routine measurement of white blood cell count and liver function tests in the absence of clinical symptoms in patients taking ATDs.<sup>1</sup> Following thyroidectomy, LT<sub>4</sub>

should be initiated at 1.6  $\mu\text{g}/\text{kg}$  per day with repeated TSH measurement at 6 to 8 weeks.<sup>1</sup>

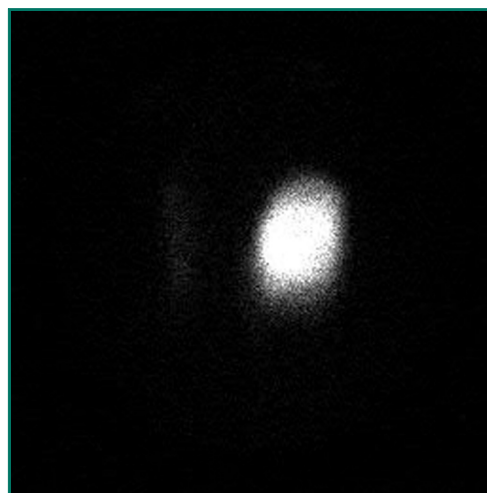
The management of GD during pregnancy is the subject of ongoing controversy.<sup>57</sup> Ideally, patients should be rendered stably euthyroid before becoming pregnant. However, if hyperthyroidism develops or persists during pregnancy, PTU is preferred during the first trimester because of the increased risk of serious birth defects associated with methimazole and carbimazole (odds ratio, 1.9 for methimazole/carbimazole vs PTU).<sup>31</sup> The risk for teratogenicity declines after week 10 of pregnancy, and thus PTU therapy is usually converted to methimazole because of the increased risk of hepatotoxicity from PTU. Given the risk of dysthyroidism associated with these therapeutic changes and the known teratogenicity of PTU itself,<sup>58</sup> these changes are still a matter of debate. Regardless of agent, the lowest dose of ATD needed to control hyperthyroidism should be used in order to prevent fetal hypothyroidism.

### Toxic Adenoma and Toxic Multinodular Goiter

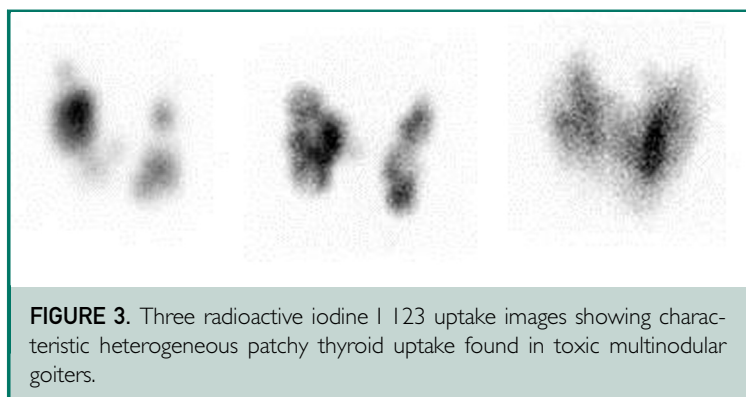
In both toxic adenoma (TA) and toxic multinodular goiter (TMNG), there is focal or multifocal hyperplasia of thyroid follicular cells with unregulated thyroid hormone production due to autonomy. Activating mutations in the TSH receptor gene seems to be the underlying mechanism resulting in increased adenylyl cyclase production independent of TSH.<sup>59,60</sup> In TA, activating mutations in the  $G\alpha$  protein have also been identified.<sup>61</sup> Toxic multinodular goiter is more common in iodine-deficient areas<sup>62</sup>; however, no clinical factors have been found to correlate with TA. Toxic multinodular goiter is also more likely in the elderly, in whom it tends to manifest as apathetic thyrotoxicosis. This presentation is defined by the absence of typical symptoms of hyperthyroidism in the presence of new-onset cardiac symptoms (heart failure and arrhythmias), cognitive changes, hypercalcemia, weakness, and lethargy.<sup>63</sup> It can be encountered in up to 15% of elderly patients in whom hyperthyroidism develops, regardless of cause.

In the setting of a palpable thyroid nodule, a nodular goiter, or antibody-negative biochemical hyperthyroidism, a thyroid uptake and scan study should be obtained. In TA, there is focal uptake in the toxic nodule (so-called hot nodule) with decreased uptake in the surrounding thyroid tissue (Figure 2). In TMNG, the scan reveals multiple areas of focal increased uptake interspersed with regions of decreased uptake that represent unaffected thyroid tissue (Figure 3).

Both TA and TMNG can be treated with either RAI or thyroid surgery. Antithyroid drugs are unable to induce cure for these conditions given their underlying mechanism for hyperthyroidism. Lifelong ATDs are also not a cost-effective option in the setting of young individuals with TA or TMNG,<sup>64</sup> but this approach might be a reasonable choice in individuals with increased surgical risk and/or limited life expectancy. For TA, risk of persistent hyperthyroidism is 6% to 18% after RAI and less than 1% after thyroid lobectomy or isthmusectomy.<sup>65</sup> There is a 20% to 55% risk of hypothyroidism with hemithyroidectomy.<sup>66,67</sup> With RAI, however, there is a progressive risk of hypothyroidism with up to 60% of patients becoming hypothyroid at 20 years after RAI.<sup>68</sup> This risk is more likely in older patients and those with thyroid



**FIGURE 2.** Radioactive iodine I 123 uptake image showing focal uptake in a toxic adenoma with decreased uptake in surrounding normal thyroid tissue.



**FIGURE 3.** Three radioactive iodine I 123 uptake images showing characteristic heterogeneous patchy thyroid uptake found in toxic multinodular goiters.

antibodies and prior treatment with ATDs.<sup>68,69</sup> Radioactive iodine is more likely to induce euthyroidism in TA as opposed to GD because the uptake of RAI is limited to the adenoma while the remaining thyroid parenchyma is suppressed and thus does not incur any severe damage from RAI. In GD, however, there is diffuse uptake throughout the gland, thereby ablating the entire thyroid.

For TMNG, the risk of persistent hyperthyroidism is 11% to 20% for RAI and less than 1% with near-total/total thyroidectomy.<sup>70,71</sup> Risk of hypothyroidism is 16% at 5 years after RAI<sup>72</sup> vs 100% with near-total/total thyroidectomy. Long-term ATD therapy is generally not recommended unless it is in the setting of decreased life expectancy or contraindications to ablative therapy (eg, pregnancy or major comorbidities). Additionally, where expertise is available, radiofrequency ablation can be used to treat TA. Radiofrequency ablation has a cure rate of 82% for thyrotoxicosis and is also associated with a substantial decrease in nodule size.<sup>73</sup> This modality is able to avoid hypothyroidism because of preservation of the surrounding thyroid tissue.

#### Amiodarone-Induced Thyroid Dysfunction

Amiodarone is the most widely prescribed antiarrhythmic agent in the United States. It has little negative inotropic activity and is, therefore, often preferred in patients with heart failure.<sup>74</sup> It contains iodine—each 100-mg amiodarone tablet provides 10 times the average daily iodine content in the American diet.<sup>75</sup> Compounding this problem is

amiodarone's long half-life of 100 days, which is due to its lipophilic nature.<sup>76</sup>

The effects of amiodarone on the thyroid are 2-fold: intrinsic drug effects and effects related to its iodine content. The combined results of these actions are that amiodarone decreases the conversion of  $T_4$  to  $T_3$ ,<sup>77</sup> inhibits the binding of  $T_3$  to its nuclear receptors,<sup>78</sup> and is directly toxic to thyroid follicular cells, resulting in a destructive thyroiditis.<sup>79</sup> In the setting of underlying thyroid disease, the excessive iodine load received after amiodarone ingestion results in either hypothyroidism (failure to escape from the Wolff-Chaikoff effect)<sup>80</sup> or hyperthyroidism (Jod-Basedow phenomenon).<sup>81</sup> There is an inversely proportional effect of dietary iodine intake on thyroid function in amiodarone-induced thyroid dysfunction. Thus, hypothyroidism is more frequent in iodine-sufficient areas (22% hypothyroidism vs 2% hyperthyroidism in Massachusetts), and hyperthyroidism is more likely in iodine-deficient areas (5% hypothyroidism vs 9.6% hyperthyroidism in Pisa, Italy).<sup>82</sup>

Although amiodarone-induced hypothyroidism is an entity that is easily managed with  $LT_4$  therapy, amiodarone-induced thyrotoxicosis (AIT) poses both diagnostic and therapeutic challenges. Amiodarone-induced thyrotoxicosis is classified as type 1 (increased thyroid hormone synthesis due to underlying GD or TMNG) and type 2 (destructive thyroiditis when the increased thyroid levels are due to release of previously stored hormone).<sup>83</sup> Type 2 AIT is now more common than type 1.<sup>63</sup> The classic adrenergic symptoms of thyrotoxicosis are often masked because of the  $\beta$ -blocking activity of amiodarone. Thus, patients usually exhibit apathetic thyrotoxicosis,<sup>63</sup> presenting with unexplained weight loss, new-onset or recurrent arrhythmias, and/or worsening ischemic heart disease or heart failure.

Differentiating type 1 from type 2 AIT is important because their treatments differ; however, both types can coexist. [Table 3](#) summarizes the differing clinical, laboratory, and imaging findings in type 1 and type 2 AIT. Our diagnostic approach is based on the clinical history and goiter assessment.

We use TRAb in addition to CFDS, which can successfully differentiate the 2 types in 80% of cases,<sup>87</sup> and have moved away from RAIU given consistently low uptake in our iodine-replete population. Technetium Tc 99m sestamibi thyroid uptake and scintigraphy have been shown in small studies (n=20<sup>89</sup> and n=15<sup>90</sup>) to correctly differentiate the type of AIT in 100% of cases as compared to CFDS or RAI<sup>88,89</sup>; however, further validation is needed.

Type 1 AIT is treated with ATDs, used at high doses and for a longer period to prevent relapse to hyperthyroidism. Potassium perchlorate has been used with some efficacy but is not available in the United States, and RAI therapy is impractical in this population. In type 2 AIT, high-dose prednisone (40-60 mg/d) is used for 1 to 3 months and then slowly tapered. When AIT type is unclear or initial response is minimal, both prednisone and methimazole should be used. Unfortunately, in about 7% of cases<sup>90</sup> there is insufficient response to medical therapy or medical therapy is not tolerated, and in those cases thyroidectomy is required. For a good success rate, it is necessary to select an experienced thyroid surgeon and have available cardiac anesthesia, given the nonnegligible mortality reported in this patient population.<sup>91</sup>

**Thyrotropin-Secreting Pituitary Adenoma**

Thyrotropin-secreting pituitary adenomas are rare, accounting for less than 1% of all pituitary adenomas (standardized incidence rate 0.03 per 100,000).<sup>92,93</sup> They are diagnosed in the setting of an inappropriately normal or high TSH level with a concomitant high T<sub>4</sub> concentration. Patients present with a small goiter and symptoms of mild hyperthyroidism. Frequently, there are also symptoms generated through local compression by the tumor (headaches and visual field defects).<sup>94</sup> This diagnosis should also be considered in patients with presumed primary hypothyroidism in whom TSH does not normalize with LT<sub>4</sub> therapy.<sup>95</sup> Pituitary imaging with magnetic resonance is the next step, and the most common presentation of a TSH-producing adenoma is a macroadenoma. Cavernous sinus invasion is present in 23%

**TABLE 3. Amiodarone-Induced Thyrotoxicosis**

Characteristic	Type 1	Type 2
Onset of symptoms after starting amiodarone (mo), median <sup>84</sup>	3.5	30
Onset of symptoms after amiodarone discontinued <sup>84</sup>	No	Yes
Goiter (diffuse or multinodular)	+	-
Thyrotropin receptor antibody	+ (GD)	-
	- (TMNG)	
Thyroglobulin <sup>85</sup>	↑↑	↑
Interleukin 6 <sup>86</sup>	↓	↑
CFDS <sup>87</sup>	↑↔	↓
Radioactive iodine uptake	↑↔↓	↓↓
<sup>99m</sup> Tc sestamibi <sup>88,89</sup>	↑↔	↓

CFDS = color flow Doppler sonography; <sup>99m</sup>Tc sestamibi = technetium Tc 99m sestamibi scintigraphy with scan; + = present; - = absent; ↑ = increased; ↑↑ = significantly increased; ↓ = decreased; ↓↓ = significantly decreased; ↑↔ = increased or normal; ↑↔↓ = increased, normal, or decreased.

of these lesions.<sup>96</sup> It can also cosecrete other pituitary hormones, most commonly growth hormone or prolactin (16% and 10%, respectively).<sup>96</sup> The treatment approach should be geared toward achieving surgical cure, with 84% of cases experiencing remission postoperatively and 17% complicated by postoperative pituitary dysfunction.<sup>96</sup>

Thyrotropin-secreting pituitary adenomas express somatostatin receptors 2 and 5,<sup>97</sup> making somatostatin analogues an effective medical option in patients who are unable to undergo surgical resection. Somatostatin analogues can be used to decrease tumor size either preoperatively or after incomplete surgical resection. It has also been associated with normalization of thyroid function.<sup>96,98,99</sup> Although some tumors also express dopamine receptors, the response to dopamine agonists has been variable.<sup>100</sup> Conventional radiotherapy or radiosurgery are other options when there is incomplete cure with surgery.<sup>101</sup> Antithyroid drugs are avoided given the expected tumor growth if the residual feedback inhibition from thyroid hormones on the tumor is eliminated.

**Hydatidiform Mole/Choriocarcinoma/  
Testicular Germ Cell Tumors**

Human chorionic gonadotropin (hCG) weakly stimulates the TSH receptor due to ligand-receptor cross-reactivity between the β subunits of hCG and TSH. Hyperthyroidism



may, therefore, be a manifestation from the severely elevated concentrations of hCG in hydatidiform mole, choriocarcinoma, and testicular germ cell tumors.<sup>102,103</sup> Radioactive iodine uptake is normal or increased. Therapy is directed to the underlying tumor; however,  $\beta$ -blockade and ATDs can be used for symptom control before definitive treatment is performed.

### Metastatic Follicular Thyroid Cancer

Follicular thyroid cancer metastasizes via hematogenous spread. These metastases contain functional thyroid tissue that rarely (about 60 reported cases in the PubMed literature<sup>104-108</sup>) can result in hyperthyroidism. Tumor cells express increased activity of type 1 and type 2 deiodinases.<sup>109</sup> Triiodothyronine thyrotoxicosis, therefore, predominates because of a combination of increased  $T_3$  secretion and increased conversion of exogenous  $T_4$  to  $T_3$ . Therefore, in these cases it will be important to obtain  $T_3$  and  $T_4$  values besides TSH measurement in order to guide the extent of thyroid hormone replacement. The intended TSH suppression can be achieved with probably much lower doses of  $LT_4$ , or at times  $LT_4$  therapy is unnecessary. Rarely, hyperthyroidism can be due to TSH receptor—stimulating antibodies.<sup>110</sup> If hyperthyroidism is manifesting beyond the intended TSH suppression despite discontinuation of  $LT_4$ , then treatment requires a multimodal approach utilizing a combination of ATDs, RAI, surgery, or radiation.

### Struma Ovarii

Struma ovarii is a mesodermal benign or malignant teratoma located in the ovary with thyroid tissue comprising more than 50% of its mass. Women most commonly present with pain or a pelvic mass (either incidental or symptomatic). Rarely, hyperthyroidism is a manifestation.<sup>111,112</sup> In the absence of a simultaneously enlarged thyroid, the mechanism is unknown but probably involves mutations leading to autonomy of the stromal tissue itself. The diagnosis should be considered in any woman with biochemical hyperthyroidism, absence of goiter, absent RAIU in the neck, and increased thyroglobulin. Pelvic ultrasonography should then be the next

step in diagnosis. Treatment is surgical removal of the tumor. Preoperative medical management includes  $\beta$ -blockers and ATDs (in the setting of moderate to severe hyperthyroidism). The stromal tissue can also harbor differentiated thyroid carcinoma. Therefore, RAI has been used as adjunctive therapy in metastatic disease.<sup>112</sup>

### Other

There are other rare causes of hyperthyroidism listed in Table 1 that are beyond the scope of this review, eg, neonatal GD, congenital hyperthyroidism, familial gestational hyperthyroidism, pituitary resistance to thyroid hormone, and hyperemesis gravidarum.

## THYROTOXICOSIS WITHOUT HYPERTHYROIDISM

### Thyroiditis

Thyroiditis refers to any disorder that results from inflammation of the thyroid tissue with resultant thyrotoxicosis due to release of preformed thyroid hormone (Table 4).

**Subacute Thyroiditis.** Subacute (granulomatous) thyroiditis, or de Quervain thyroiditis, is thought to be due to a viral infection or a postviral inflammatory process. Presumably the infection-related antigen possesses structural similarity with thyroid follicular cells. Binding of the antigen to HLA-B35 on macrophages results in activation of cytotoxic T cells. These T cells then invade the thyroid, causing thyroid inflammation and proteolysis of stored thyroglobulin. There is a resultant surge in  $T_3$  and  $T_4$  values due to their release, causing symptoms of thyrotoxicosis. New thyroid hormone production ceases because of underlying thyroid gland inflammation and lack of TSH stimulation, which is suppressed due to the high concentrations of  $T_3$  and  $T_4$ . Often, the thyrotoxicosis is followed by a period of hypothyroidism until the thyroid gland recovers and TSH increases. In most cases, thyroid hormone synthesis resumes and euthyroidism is eventually achieved after a period of 2 to 3 months.

The presenting symptom is usually anterior neck pain following an infection,

**TABLE 4. Forms of Thyroiditis<sup>a</sup>**

Subtype	History	Etiology	TPO antibodies	ESR	RAIU
Subacute	Anterior neck pain following viral infection	Postviral inflammation due to antigen similarity with thyroid follicular cells	Low titer or negative	High	Low
Painless	Absence of neck pain, family history of thyroid disorder	Likely autoimmune	High titer positive	Low	Low
Postpartum	Pregnancy or miscarriage within the past year, absence of neck pain, family history of thyroid disorder	Likely autoimmune	High titer positive	Low	Low
Drug induced	History of offending drug, family history of thyroid disorder	Induced thyroid autoimmunity or direct toxic effect on thyroid	Positive or negative	Low	Low
Infectious/suppurative	Fever, neck pain, immunocompromised	Acute bacterial thyroid infection	Negative	High	Normal
Riedel/fibrous <sup>b</sup>	Neck tightness, dysphagia, hoarseness, diffusely hard goiter	Extensive fibrosis with lymphocyte and eosinophil infiltration	Positive, high titer	Normal	Low or normal

<sup>a</sup>ESR = erythrocyte sedimentation rate; RAIU = radioactive iodine uptake; TPO = thyroid peroxidase.

<sup>b</sup>This form of thyroiditis is not associated with thyrotoxicosis at any point but rather with a slowly progressive form of hypothyroidism.

occasionally associated with fever, fatigue, and myalgia. The thyroid is enlarged and tender, and there are signs of thyrotoxicosis. In addition to a suppressed TSH concentration with elevated T<sub>4</sub> and T<sub>3</sub> levels, laboratory findings include the absence of thyroid antibodies (can occasionally be present in the hypothyroid phase), increased thyroglobulin, and elevated erythrocyte sedimentation rate or C-reactive protein. Radioactive iodine uptake is diffusely low, an essential element in the diagnosis of thyroiditis, and CFDS reveals decreased vascularity.

Treatment is supportive because the disease is self-limiting. Nonsteroidal anti-inflammatory agents can be used for neck pain. If this treatment is insufficient, prednisone can be given, which relieves the pain within a few days. It then should be tapered off and the dose titrated in response to pain. β-Blockade is helpful for symptoms of thyrotoxicosis. During the phase of hypothyroidism, a short course of LT<sub>4</sub> may be needed for moderate to severe symptoms. Because the thyroid function usually recovers, LT<sub>4</sub> should be tapered off and thyroid function should be monitored every 3 to 4 weeks until euthyroidism resumes.

**Painless Thyroiditis.** Painless thyroiditis, which is also called *silent thyroiditis* or

*lymphocytic thyroiditis*, accounts for approximately 0.5% to 5% of cases of hyperthyroidism in iodine-sufficient areas.<sup>7,113</sup> In this category, we do not include the cases of thyroiditis diagnosed within the first year postpartum. Painless thyroiditis is thought to be part of the spectrum of autoimmune thyroid disorders, affecting more women than men and often occurring in the presence of thyroid antibodies or a family history of thyroid autoimmunity.<sup>114</sup> The diagnosis relies on biochemical thyrotoxicosis, a small nontender thyroid gland, and absence of pathognomonic signs of GD. The erythrocyte sedimentation rate is normal, and RAIU is decreased. Eventually, 20% of patients with painless thyroiditis will become hypothyroid.<sup>115</sup> It has a clinical course similar to that of subacute thyroiditis with hyperthyroidism initially resulting from thyroid gland destruction, then hypothyroidism from decreased thyroid hormone stores and synthesis, and then either normal thyroid function resumes or the patient remains hypothyroid. Treatment is supportive, consisting mainly of β-blockade unless hypothyroidism persists.

**Postpartum Thyroiditis.** Postpartum thyroiditis occurs in 5% to 7% of women within the first few months after delivery.<sup>116</sup> It is more common in women with other

autoimmune disorders, TPO antibodies, or a family history of thyroid disease.<sup>114</sup> Pathologic findings reveal lymphocytic infiltration, which suggests that it is a variant of Hashimoto thyroiditis.<sup>117</sup> As with other forms of thyroiditis, the typical 3 phases are to be expected, starting with thyrotoxicosis 1 to 6 months after delivery. There is a 70% risk of recurrent postpartum thyroiditis after the first episode.<sup>118</sup> Permanent hypothyroidism can eventually occur in up to 50% of women<sup>119</sup> and is more likely in multiparous women or after spontaneous abortion.<sup>120</sup>

The diagnosis can be made in any woman within 1 year of pregnancy, and it follows the approach described for silent thyroiditis. In the breastfeeding period, thyroid uptake and scan studies are used sparingly. Because iodine is secreted in breast milk, nursing mothers will need to pump and discard milk for 2 days after RAI I 123 is administered. Treatment is supportive, as described for painless thyroiditis. Prevention of postpartum thyroiditis in women with high TPO antibody titers has been tried with selenium therapy, and although preliminary studies have found this intervention beneficial,<sup>121</sup> confirmatory studies are not yet available.

**Drug-Induced Thyroiditis.** There are a number of drugs that are known to cause thyroiditis, some with less prominent utilization now than in the past (interferon alfa, interleukin 2) while others are still a consistent choice for their main indication (amiodarone, lithium). These drugs are by now well known to most practitioners. However, new drugs have been developed recently that have consistently demonstrated an ability to induce inflammation and destruction of the thyroid parenchyma through a number of mechanisms, primarily autoimmune and/or ischemic. The most commonly encountered classes of these new drugs are tyrosine kinase inhibitors and immune checkpoint inhibitors.

Tyrosine kinase inhibitors are used to treat many types of cancer (eg, renal cell carcinoma, gastrointestinal tumors, and thyroid cancer), and they have been associated with a form of destructive thyroiditis. Best known

for this adverse effect are sunitinib (prevalence 10%)<sup>122</sup> and sorafenib (prevalence 3%),<sup>123</sup> and thyroiditis related to these agents can occur as early as 6 weeks into therapy. Repeated cycles of therapy have been followed by recurrent episodes of thyroiditis and then by permanent hypothyroidism.<sup>124</sup>

Checkpoint inhibitor immunotherapy targeting cytotoxic T-lymphocyte antigen 4 (eg, ipilimumab) and programmed cell death 1 receptor (eg, pembrolizumab) are excellent therapies for metastatic melanoma. They are, however, associated with a destructive thyroiditis. Thyrotoxicosis was observed in 6% to 22%<sup>125,126</sup> of patients treated with pembrolizumab, occurring at a median of 6 weeks after initiation of therapy.<sup>126</sup> The exact mechanism is unclear; however, it may be due to T-cell-, natural killer cell-, or monocyte-mediated pathways.<sup>127</sup>

For all these entities, removal of the offending agent must be weighed against the benefit that the drug provides for the preexistent disease. The therapy is mainly supportive by controlling the symptoms of thyrotoxicosis with  $\beta$ -blockers and initiating  $LT_4$  when hypothyroidism develops.

**Other Forms of Thyrotoxicosis Without Hyperthyroidism.** There are other rare causes of thyrotoxicosis listed in [Table 1](#) that are beyond the scope of this review (acute infectious thyroiditis, radiation-induced thyroiditis, and thyrotoxicosis associated with adenoma infarction).

### Exogenous Thyrotoxicosis

Exogenous hyperthyroidism is due to intentional (thyrotoxicosis factitia) or accidental ingestion of excessive amounts of thyroid hormone. In conditions such as differentiated thyroid cancer, there is intentional overdosing by clinicians aiming to solely suppress TSH (while attempting to avoid hyperthyroxinemia) and hopefully prevent or decrease tumor growth.<sup>128</sup> Patients may overdose intentionally to achieve the adverse effect of weight loss or to increase energy or because of a psychiatric disorder. There may be unintentional overdosing with weight-reducing supplements<sup>129</sup> or

thyroid health supplements<sup>130</sup> or the occurrence of “hamburger thyroiditis” (consumption of beef contaminated with thyroid tissue due to incorporation of the cow’s neck tissue in the patty).<sup>131</sup>

Laboratory findings reveal biochemical thyrotoxicosis, low thyroglobulin level, and decreased RAIU. Fecal T<sub>4</sub> can be measured in difficult cases.<sup>132</sup> Treatment includes  $\beta$ -blockade, iopanoic acid (not available in the United States), which decreases T<sub>4</sub> to T<sub>3</sub> conversion, and cholestyramine, which binds T<sub>4</sub> and T<sub>3</sub> in the intestine.<sup>133</sup> In extreme cases, therapeutic plasmapheresis can be used to achieve a rapid decrease in thyroid hormone levels if the aforementioned measures are not effective.

#### PITFALLS IMPACTING ASSESSMENT OF THE THYROTOXIC STATE

The diagnosis of thyrotoxicosis is fairly straightforward in most cases. However, there are a number of instances in which the diagnosis should be carefully considered. These scenarios can present with a discrepancy between a biochemical picture of thyrotoxicosis and a clinical presentation that does not support it. Alternatively, there might be notable inconsistencies between the various thyroid parameters combined with variable clinical presentations, neither conclusive for thyroid dysfunction.

One scenario relates to the impact of biotin on thyroid test results.<sup>134,135</sup> Currently, biotin is frequently used for touted benefits regarding skin, hair, and nail health. Biotinylated products are also part of a number of hormonal assays, specifically TSH, free T<sub>4</sub> and T<sub>3</sub>, and TRAb. The way biotin impacts these assays (suppressing TSH value and elevating T<sub>4</sub>, T<sub>3</sub>, and TRAb) can result in a spurious diagnosis of GD. Therefore, in order to avoid misdiagnosis, we recommend performing thyroid tests after patients have not taken biotin for a minimum of 12 hours and preferably 24 hours. It seems that the dose of biotin that will clearly impact the thyroid test results is 10 mg/d or higher, but lower doses might be problematic as well. Obviously, the role of patient and physician education about proper methodology for

thyroid testing is paramount in avoiding this pitfall.

Another pitfall we noted in the diagnosis of hyperthyroidism relates to the use of thyroid scan and uptake. It is important that this test be interpreted in view of the simultaneous TSH value as well as through the appreciation of iodine status. In patients with elevated iodine uptake and normal TSH/T<sub>3</sub>/T<sub>4</sub> concentrations, iodine deficiency should be suspected rather than endogenous hyperthyroidism. These patients will have a symmetric uptake that is elevated based on our reference range but is reflective of their iodine deficit. It is thus pertinent that in countries where iodine deficiency is prevalent, the normal value for iodine uptake is much higher than in the United States. The explanation for the iodine deficit in patients residing in iodine-sufficient areas usually relates to some very particular dietary habits that are pertinent for avoidance of iodine-containing products. All ATD therapies should be avoided in these cases, and iodine supplementation should be initiated.

Occasionally, thyrotoxicosis is diagnosed on the basis of a suppressed TSH level alone, most commonly during follow-up of patients receiving thyroid hormone replacement therapy. In these cases, a suppressed TSH level is interpreted as iatrogenic thyrotoxicosis, and the dose of LT<sub>4</sub> is decreased. In our experience, this is noted when patients with central hypothyroidism change medical providers. However, physicians should also consider the possibility that an additional pathologic process affecting TSH production (eg, hypophysitis, pituitary tumor, pituitary apoplexy) might have developed in patients with preexistent primary hypothyroidism. A similar situation is noted in patients who use high-dose corticosteroids, which can suppress TSH-releasing hormone and TSH concentrations<sup>136,137</sup> leading to a state of central hypothyroidism. This is a transient situation that will resolve with the discontinuation of corticosteroids. Therefore, a clinical correlation for the suppressed TSH should be sought, and if it is not indicative of thyrotoxicosis, further exploration of thyroid status with T<sub>3</sub> and T<sub>4</sub> measurements

should be sought in order to make the correct diagnosis.

### UNRESOLVED QUESTIONS AND POTENTIAL FUTURE DEVELOPMENTS

In recent years, there have been a number of attempts to revamp the approach to hyperthyroidism, particularly to GD. Many are targeting the immune system. Rituximab has been tried, but the results were not impressive<sup>138</sup> and it has not been pursued further. CFZ533 targets CD40-CD154 interaction and has been tested in a phase 2 clinical trial (NCT02713256) with results yet to be reported. Other studies are testing the efficacy of a tolerogenic vaccine to prevent TSH receptor antibody formation, and another uses a monoclonal antibody that is a TSH receptor blocker. Some approaches to hyperthyroidism therapy are ultrasound based, such as high-intensity focused ultrasound and radiofrequency ablation. All these therapies will have to undergo further evaluations before they can be employed routinely in decreasing thyroid hormone production.

### CONCLUSION

The diagnostic evaluation of thyrotoxicosis should start from the clinical picture and then add biochemical testing, nuclear medicine data, and ultrasound imaging, as appropriate. Biotin is being increasingly acknowledged as a factor leading to spurious biochemical results and should be considered in laboratory interpretation. Distinguishing increased thyroid hormone production from thyroiditis remains essential in therapeutic selection. Graves disease and TMNG are the dominant causes of hyperthyroidism, and for GD, we are seeing an increasing tendency to use ATDs, sometimes long-term, with a simultaneous decrease in the use of RAI. Regarding thyroiditis, there remain multiple etiologies to be considered, and some of the new oncological drugs have added to our differential diagnosis. These developments might also shed more light on the mechanisms involved in thyroid autoimmunity. This new information should spur the ongoing effort of identifying new agents that can tackle thyrotoxicosis, particularly GD, in a modern way by addressing its pathophysiology.

Thus, hopefully the long-overdue therapeutic paradigm shift for this entity will reach the horizon.

**Abbreviations and Acronyms:** AIT = amiodarone-induced thyrotoxicosis; ATD = antithyroid drug; CFDS = color flow Doppler sonography; GD = Graves disease; GO = Graves orbitopathy; hCG = human chorionic gonadotropin; LT<sub>4</sub> = levothyroxine; PTU = propylthiouracil; RAI = radioactive iodine; RAIU = RAI uptake; T<sub>3</sub> = triiodothyronine; T<sub>4</sub> = thyroxine; TA = toxic adenoma; TMNG = toxic multinodular goiter; TPO = thyroid peroxidase; TRAB = thyrotropin receptor antibody; TSH = thyrotropin

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