

**CME CREDIT** **EDUCATIONAL OBJECTIVE:** Readers will follow up the finding of a low thyrotropin (TSH) level with appropriate diagnostic investigations

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# Approach to a low TSH level: Patience is a virtue

## ABSTRACT

Confronted with a low serum level of thyrotropin (thyroid-stimulating hormone, TSH), physicians should not jump to the conclusion that it is due to a hyperthyroid state, as other conditions and some drugs can be associated with a TSH level that is slightly low (0.1–0.4  $\mu\text{IU/mL}$ ) or frankly suppressed ( $< 0.1 \mu\text{IU/mL}$ ). This review discusses how to approach a low TSH, stressing the frequent need to reassess thyroid function before making a diagnosis, the underlying processes and the drugs that can be responsible, and the degree of TSH suppression and its role in the evaluation.

## KEY POINTS

A low TSH value should always be followed up by measuring the thyroid hormones, ie, thyroxine ( $T_4$ ) and triiodothyronine ( $T_3$ ).

Serum levels of free thyroid hormones should be used when interpreting an abnormal TSH level, especially in the acute and inpatient settings.

A low TSH level is not always the result of suppression by elevations in circulating thyroid hormones.

A low TSH level in the setting of normal levels of free thyroid hormones should always be reassessed in 4 to 6 weeks before making a diagnosis.

Overt hyperthyroidism is usually associated with a frankly suppressed TSH ( $< 0.1 \mu\text{IU/mL}$ ).

A 34-YEAR-OLD WOMAN presents to the outpatient endocrinology clinic 4 months postpartum. She says that 2 months ago she developed palpitations, heat intolerance, and difficulty sleeping. Her primary care physician diagnosed postpartum thyroiditis after laboratory evaluation revealed that her thyrotropin (thyroid-stimulating hormone, TSH) level was low at 0.005  $\mu\text{IU/mL}$  (reference range 0.4–5.5), and that her free thyroxine ( $T_4$ ) level was elevated at 2.4 ng/dL (reference range 0.7–1.8). She was prescribed atenolol (Tenormin) to treat the symptoms.

On follow-up testing 6 weeks later, her TSH level had risen, but it was still low at 0.085  $\mu\text{IU/mL}$ , and her free  $T_4$  level was now low at 0.6 ng/dL. She was referred to an endocrinologist for further management.

How should this patient be further evaluated and managed?

## LOW TSH HAS MANY CAUSES

A low serum TSH level, ie, less than 0.4  $\mu\text{IU/mL}$  ( $\mu\text{IU/mL} = \text{mIU/L} = \text{mU/L}$ ) can result from a variety of conditions that must be included in the differential diagnosis—not just overt or subclinical hyperthyroidism (FIGURE 1). In diagnosing the correct cause, patience is a virtue.

## Follow up the finding of a low TSH by measuring free $T_4$ and free $T_3$

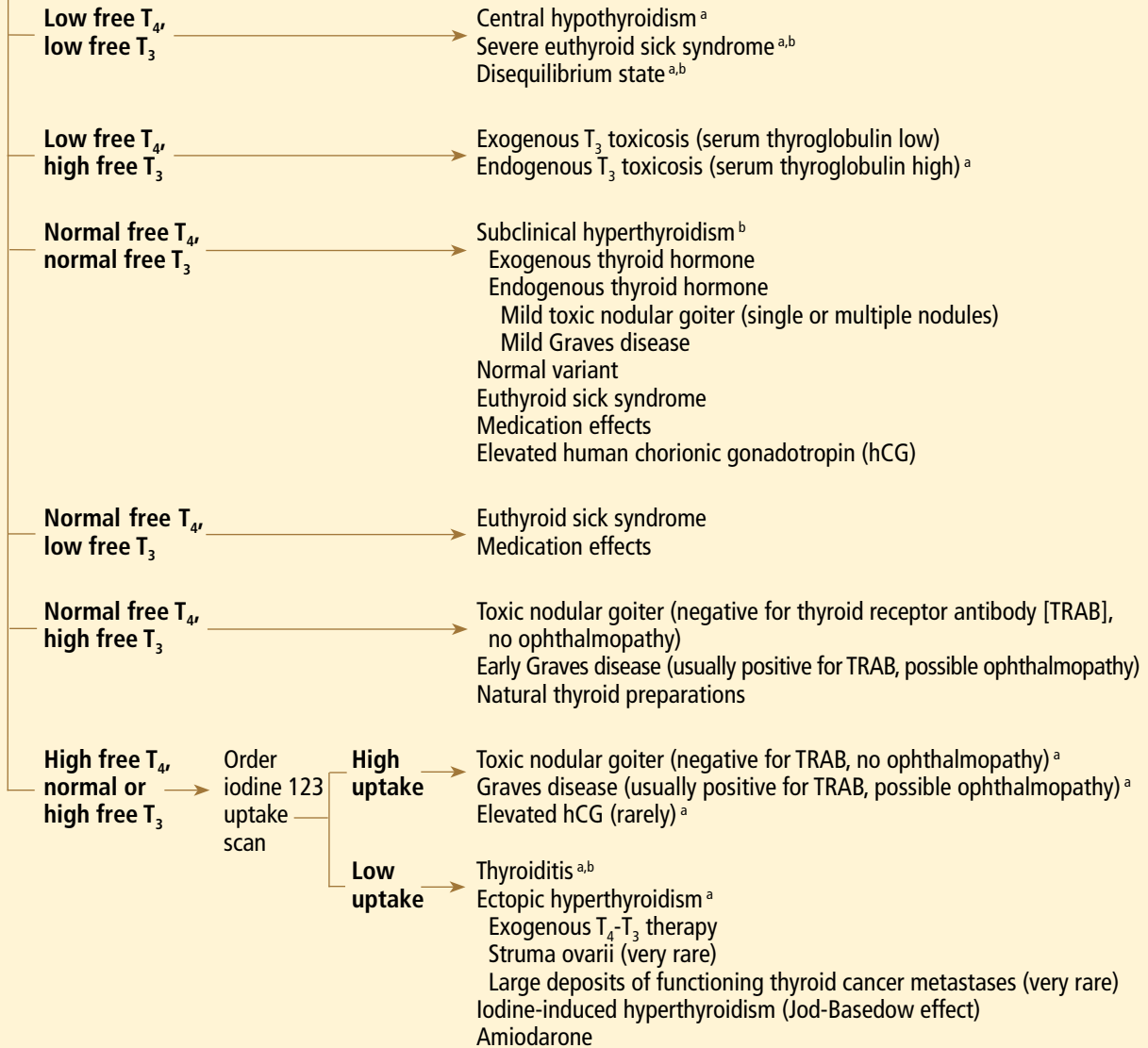
The finding of a low TSH level should always be followed up by measuring the thyroid hormones, ie,  $T_4$  and triiodothyronine ( $T_3$ ).

The levels of free  $T_4$  and free  $T_3$  should be used, not total levels, when interpreting an abnormal TSH value. This especially applies in the acute and inpatient settings, in

**Approach to the finding of a low thyrotropin level**

Low thyrotropin (thyroid-stimulating hormone, or TSH)

Measure free thyroxine ( $T_4$ ) and free triiodothyronine ( $T_3$ )



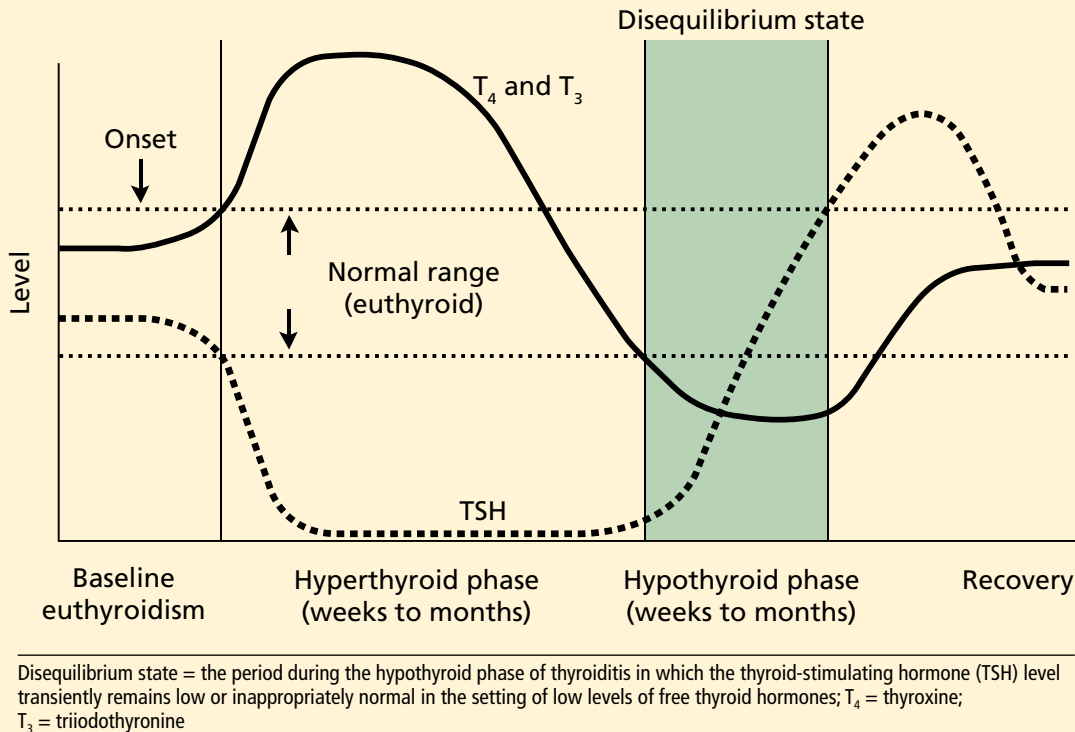
<sup>a</sup> Refer to an endocrinologist if suspected; <sup>b</sup> Repeat tests for TSH, free  $T_4$ , and free  $T_3$  in 6–8 weeks. See text for details

**FIGURE 1**

which many patients are malnourished and consequently have low serum levels of thyroid-binding globulin and albumin. In this situation, total  $T_4$  and  $T_3$  levels may be low and not accurately represent a patient's true thyroid status. Likewise, in women who are

pregnant or taking an estrogen-containing contraceptive, the total  $T_4$  and  $T_3$  levels may be high, secondary to an increase in thyroid-binding globulin synthesis, but the free  $T_4$  and free  $T_3$  are normal (in the absence of a pathologic process).

## Natural history of thyroid function tests in patients with thyroiditis



**FIGURE 2**

However, depending on the analytical method, even measurements of the free hormones may be affected by the protein changes that occur during severe illness or pregnancy. Also, some drugs can affect free hormone levels by displacing the hormones from their binding proteins.

Most commercial laboratories estimate the levels of free thyroid hormones by indirect methods. Short of measuring the free thyroid hormones directly using equilibrium dialysis and ultrafiltration (the gold standard), no test or assay is 100% accurate. Even the determination of free hormone levels can be flawed if the assay is unreliable. Some clinicians still prefer the free thyroid index (FTI) and  $T_3$  or  $T_4$  resin uptake to assess free  $T_4$ , and the total  $T_3$  to assess  $T_3$  status.

The degree of TSH suppression should also be taken into account. A frankly suppressed TSH level ( $< 0.1 \mu\text{IU/mL}$ ) would favor overt thyrotoxicosis in the correct clinical context (ie, if the levels of free  $T_4$ , free  $T_3$ , or both were normal or high).

FIGURE 1 outlines how to interpret a low TSH level and formulate the appropriate diagnosis and plan. In this process, it is crucial to consider the patient's history, to note signs or symptoms of thyroid disease (hyperthyroidism or hypothyroidism), and to ask about medication exposure. Furthermore, repeating the thyroid function tests (and reviewing previous values) to observe the trend is consistently invaluable when deriving a diagnosis.

### ■ LOW TSH, LOW FREE $T_4$ , LOW FREE $T_3$

The history of present illness (especially if the illness is prolonged and critical), a review of previous thyroid function tests, and, sometimes, a complete evaluation of the remaining hypothalamic-pituitary axes are crucial in correctly interpreting this combination of thyroid function tests. Clinical judgment is required, and referral to an endocrinologist is warranted. The diagnostic possibilities are:

**Central hypothyroidism.** A low TSH level is not always due to suppression caused

**Use free  $T_4$  and free  $T_3$  levels, not total levels, when evaluating a low TSH**

by high thyroid hormone levels, other conditions, or medications. If thyroid hormone levels are low, a low TSH value can be the result of a central process (hypothalamic or pituitary or both).

**Severe euthyroid sick syndrome** (also called “nonthyroidal illness” or “low  $T_3$  syndrome”). In this condition, the free  $T_3$  level is usually low, and in severe cases the free  $T_4$  level can also be low.<sup>1,2</sup>

**Disequilibrium state**, which is seen in the hypothyroid phase of resolving thyroiditis (FIGURE 2). This will be discussed later, in the section on thyroiditis.

### ■ LOW TSH, LOW FREE $T_4$ , HIGH FREE $T_3$

#### **$T_3$ toxicosis from an exogenous source**

The combination of low TSH, low free  $T_4$ , and elevated free  $T_3$  concentrations is consistent with ingestion of supratherapeutic doses of exogenous  $T_3$ , ie, liothyronine (Cytomel).

Rarely is  $T_3$  therapy used alone to treat hypothyroidism. An exception is in patients who undergo thyroid hormone withdrawal in anticipation of radioactive iodine treatment after having undergone total thyroidectomy for differentiated thyroid cancer.

$T_3$  therapy, when used, is often given in combination with  $T_4$  therapy, either levothyroxine (Synthroid and others) or as part of a  $T_4$ - $T_3$  natural thyroid preparation derived from porcine thyroid tissue (Armour Thyroid, Nature-Throid). Natural thyroid preparations may contain large amounts of  $T_3$ , and when they are given in supratherapeutic doses, they can cause a similar profile (low TSH, low free  $T_4$ , and elevated free  $T_3$ ). However, the free  $T_4$  level is usually in the normal range because the preparations also contain  $T_4$ .

#### **$T_3$ toxicosis from an endogenous source**

Sometimes the thyroid gland produces disproportionately large amounts of  $T_3$ , usually from an autonomous nodule. Although the free  $T_4$  level may be low in this situation, it is usually in the normal range.

Serum thyroglobulin can be assayed to help determine whether the source of excess  $T_3$  is exogenous (in which case the thyroglobulin level is low) or endogenous (in which case the thyroglobulin is elevated). If it is endogenous,

the patient should be referred to an endocrinologist for further evaluation.

### ■ LOW TSH, NORMAL FREE $T_4$ , NORMAL FREE $T_3$

#### **Subclinical hyperthyroidism**

Subclinical hyperthyroidism is defined as low TSH, normal free  $T_4$ , and normal free  $T_3$  levels. Symptoms of hyperthyroidism such as fatigue, insomnia, weight loss, palpitations, tremor, or heat intolerance generally play a role in whether therapy is considered, but not in making the diagnosis of subclinical hyperthyroidism. To make the correct diagnosis, it is crucial to confirm that this pattern of test results persists by repeating these tests over the next few months.

**Exogenous thyrotoxicosis**, by far the most common form of subclinical thyrotoxicosis, results from taking levothyroxine ( $T_4$ ) or liothyronine ( $T_3$ ), or both, either in unintentional supratherapeutic doses in patients with hypothyroidism or in intentionally high doses to suppress TSH in patients with a history of differentiated thyroid cancer.

**Endogenous thyrotoxicosis.** Subclinical hyperthyroidism from an endogenous cause is the result of an underlying pathophysiologic process, the same processes responsible for overt states of hyperthyroidism (eg, Graves disease, toxic nodular thyroid disease) (see the discussion of overt hyperthyroidism in a later section).

The course of endogenous subclinical hyperthyroidism depends on the underlying cause and on the level of TSH suppression.<sup>3-5</sup> Subclinical hyperthyroidism secondary to a multinodular goiter is estimated to progress to overt hyperthyroidism in about 5% of patients per year,<sup>6</sup> but in patients with nodular thyroid disease and TSH levels of 0.1  $\mu$ IU/mL or lower, one study reported progression to overt hyperthyroidism in approximately 10% of patients per year.<sup>3</sup>

The risk of subclinical Graves disease progressing to overt hyperthyroidism has been difficult to estimate, given the relapsing and remitting nature of the disease. Rosario<sup>3,4</sup> reported that subclinical Graves disease progressed to overt hyperthyroidism in 2 years in 6 (40%) of 15 patients who had TSH levels

**Consequences of subclinical hyperthyroidism: atrial fibrillation, bone loss**

lower than 0.1  $\mu\text{IU/mL}$ , but in no patients who had TSH levels of 0.1 to 0.4  $\mu\text{IU/mL}$ . These patients were younger than 65 years. In a group age 60 and older with endogenous subclinical hyperthyroidism and a TSH level between 0.1 and 0.4  $\mu\text{IU/mL}$ , Rosario<sup>4</sup> reported that progression to overt hyperthyroidism was uncommon, occurring in about 1% of patients per year.

Thus, periodic reassessment of thyroid function tests in patients with subclinical hyperthyroidism is crucial in monitoring for disease progression, especially in those with frankly suppressed TSH values ( $< 0.1 \mu\text{IU/mL}$ ).

Adverse outcomes associated with subclinical hyperthyroidism are mainly cardiac arrhythmias (atrial fibrillation) and accelerated loss of bone mineral density.

Cooper<sup>7</sup> notes that definitive treatment (radioactive iodine ablation, antithyroid drugs, or surgery) “seems reasonable” for older patients (age  $> 60$  years) with a TSH level lower than 0.1  $\mu\text{IU/mL}$  and for certain patients with TSH levels of 0.1 to 0.4 who are at high risk, eg, those with a history of heart disease, osteoporosis, or symptoms of hyperthyroidism.

### Normal variant

The normal range for TSH, as for other substances, is defined as the mean value in the general population plus or minus 2 standard deviations. This range includes 95% of the population, so that 2.5% of people have a level higher than this range, and 2.5% have a level lower than this range.

But some people with lower levels of TSH, especially in the range of 0.1 to 0.4  $\mu\text{IU/mL}$  (3 standard deviations below the mean) are actually euthyroid. These people have historically been classified as having subclinical hyperthyroidism, as there is no means of differentiating these “normal” euthyroid people from people with asymptomatic subclinical hyperthyroidism. They need to be followed, since they may have true subclinical hyperthyroidism that may manifest symptomatically in the future, possibly warranting treatment.

### Euthyroid sick syndrome

Euthyroid sick syndrome is common during critical illness. However, thyroid disease is

common in the general population, and often no test results from before the onset of a critical illness are available to help the clinician separate overt thyroid disease from euthyroid sick syndrome. Furthermore, patients are often unable to provide a history (or to relate their symptoms) of overt thyroid disease, making abnormal thyroid function tests difficult to interpret in the hospital. When previous values are available, they can be invaluable in correctly interpreting new abnormal results.

Thyroid function test values in euthyroid sick syndrome can vary depending on the severity of illness. A low free  $T_3$ , a normal free  $T_4$ , and a low-normal TSH are the most common abnormalities seen in euthyroid sick syndrome. The free  $T_3$  level is low because of decreased peripheral conversion of  $T_4$  to  $T_3$  during critical illness. However, euthyroid sick syndrome can present with a spectrum of abnormal thyroid function tests, further complicating interpretation and diagnosis. Serum TSH levels have been reported to be normal in about 50%, low in 30%, and high in 12% of patients with nonthyroidal illness.<sup>8</sup> However, marked suppression of serum TSH ( $< 0.1 \mu\text{IU/mL}$ ) was observed only in about 7% of patients, mainly in those whose clinical picture was confounded by medications (dopamine or corticosteroids, or both) that have independent TSH-lowering effects (see below).<sup>8</sup>

### Drugs that suppress TSH

Many drugs used in the hospital and intensive care unit can alter thyroid function tests independently of systemic illness, further complicating the clinical picture.

**Glucocorticoids**, in high doses, have been shown to transiently suppress serum TSH.<sup>9,10</sup>

**Octreotide** (Sandostatin) and other somatostatin analogues also transiently suppress TSH.<sup>11–14</sup> However, these drugs (and glucocorticoids) do not appear to result in central hypothyroidism.<sup>10,15–17</sup>

**Dopamine**, given in pharmacologic doses for a prolonged time, has been shown to reduce the serum TSH level in both critically ill and normal healthy people.<sup>18</sup>

**Dobutamine** (Dobutrex) in pharmacologic doses has been likewise shown to lower TSH levels, although the serum TSH level was noted to remain within the normal range in those

**Previous test results can be invaluable when interpreting new abnormal results**

who had a normal TSH value at baseline.<sup>19</sup>

**Amiodarone.** Although most patients who take amiodarone (Cordarone, Pacerone) remain euthyroid, the drug can cause hypothyroidism or hyperthyroidism. Initially, amiodarone usually causes a decrease in  $T_3$  via inhibition of 5'-deiodinase, with a transient reciprocal increase in TSH.<sup>20</sup>

When amiodarone induces thyrotoxicosis, the condition can be subclinical, manifested by a low TSH in the setting of normal levels of thyroid hormones, or as overt thyrotoxicosis with a low TSH and elevated levels of thyroid hormones. See further discussion below on amiodarone's effects on thyroid function.

Patients taking drugs that lower TSH are often critically ill and may also have a component of euthyroid sick syndrome, resulting in a mixed picture.

**Elevated human chorionic gonadotropin**

The alpha subunit of human chorionic gonadotropin (hCG) is homologous to the alpha subunit of TSH. Thus, hCG in high concentrations has mild thyroid-stimulating activity.

The serum hCG concentration is highest in the first trimester of pregnancy and hCG's thyroid-stimulating activity can suppress the serum TSH level, but in most cases the TSH level remains within the "normal range" of pregnancy.<sup>21,22</sup> The hCG levels observed during the first trimester of pregnancy are usually associated with a low TSH and normal free thyroid hormone levels. In pregnant women who are not on  $T_4$  therapy for hypothyroidism, a persistently suppressed TSH (< 0.1  $\mu$ IU/mL) after the first trimester or elevations of the free thyroid hormones at any point during pregnancy suggest that the suppressed TSH is secondary to autonomous thyroid function, as seen in Graves disease and toxic nodular goiters, warranting further investigation. Iodine radioisotope imaging studies are forbidden during pregnancy.

If the hCG concentration is markedly elevated and for a prolonged time, as in hyperemesis gravidarum and gestational trophoblastic disease (hydatidiform mole, a benign condition, and choriocarcinoma, a malignant condition), overt hyperthyroidism can develop, with elevated free  $T_4$  and free  $T_3$ .<sup>21,23</sup>

**If excess  $T_3$  is exogenous, thyroglobulin is low; if endogenous, thyroglobulin is elevated**

■ **LOW TSH, NORMAL FREE  $T_4$ , LOW FREE  $T_3$**

**Euthyroid sick syndrome and/or medication effect.** When the TSH level is low secondary to euthyroid sick syndrome or a drug, or both, the free  $T_3$  level is usually found to be also low, which may be solely related to a component of euthyroid sick syndrome or secondary to the drugs themselves, as drugs such as corticosteroids and amiodarone inhibit the conversion of  $T_4$  to  $T_3$ .

■ **LOW TSH, NORMAL FREE  $T_4$ , HIGH FREE  $T_3$**

**Toxic nodular goiter vs early Graves disease**

If the free  $T_3$  is elevated and the TSH is low (suppressed), even in the absence of symptoms, a diagnosis of subclinical hyperthyroidism would be inappropriate, because by definition the free  $T_4$  and free  $T_3$  levels must be normal for a diagnosis of subclinical hyperthyroidism. The diagnostic possibilities are toxic nodular goiter and early Graves disease.

The combination of high  $T_3$ , suppressed TSH, and normal  $T_4$  is usually associated with toxic nodular goiter, whereas  $T_3$  and  $T_4$  are typically both elevated in Graves disease (although  $T_3$  is usually more elevated than  $T_4$ ).<sup>24</sup>

The patient should undergo iodine 123 nuclear imaging ("iodine uptake and scan"). Diffuse uptake of iodine 123 supports the diagnosis of Graves disease; patchy and nodular areas of increased iodine 123 uptake support the diagnosis of a toxic nodular goiter (FIGURE 3).

The patient should also be tested for TSH receptor antibodies (TRAB), both stimulating and blocking, which are very specific for Graves disease.

**Natural thyroid preparations**

Natural thyroid preparations, which can contain large amounts of  $T_3$ , can also yield the combination of normal free  $T_4$  and high free  $T_3$ . Since these preparations contain both  $T_4$  and  $T_3$ , they usually result in low TSH, normal free  $T_4$ , and elevated free  $T_3$  levels when given in supratherapeutic doses. However, if these preparations are consumed in large enough quantities, both the free  $T_4$  and free  $T_3$  can be elevated. This is in contrast to supratherapeutic monotherapy with  $T_3$  (liothyronine), which usually results in low TSH, low free  $T_4$ , and high free  $T_3$ .

## Graves disease



## Toxic nodular goiter



**FIGURE 3.** Left, an iodine 123 scan from a patient with Graves disease. Note the diffuse homogenous uptake of the thyroid gland. Right, an iodine 123 scan from a patient with a toxic multinodular goiter. Note the nodular areas of increased intensity with suppression (low uptake) of the surrounding thyroid tissue.

### ■ LOW TSH, HIGH FREE $T_4$ , NORMAL OR HIGH FREE $T_3$

If the free  $T_4$  level is high, the free  $T_3$  level is usually high as well. Patients should undergo iodine 123 nuclear imaging.

### If iodine 123 uptake is high

**Graves disease vs toxic nodular goiter.** If iodine 123 uptake is high, a low (suppressed) TSH level, in conjunction with elevations of the free thyroid hormones, is consistent with overt hyperthyroidism secondary to autonomous (TSH-independent) thyroid function.

Graves patients usually test positive for TRAB, and they may have related ophthalmopathy, whereas patients with toxic nodular goiter are TRAB-negative and do not have Graves ophthalmopathy.<sup>24-27</sup>

Patients with either Graves disease or toxic nodular goiter have increased iodine 123 uptake; however, the pattern of uptake in Graves disease is diffuse, whereas it is patchy or nodular when toxic nodular goiter is the underlying etiology (FIGURE 3).<sup>24,27</sup> Complicating matters, the pattern of uptake in Graves disease may be patchy if the patient has been pretreated with antithyroid drugs such as propylthiouracil or methimazole (Tapazole).

Review of the patient's history is important, as a recent iodine load (eg, intravenous contrast medium that contains iodine) can transiently worsen thyrotoxicosis while causing the iodine 123 uptake to be low. The reason for the low uptake is that the gland

becomes saturated with “cold” (nonradiolabeled) iodine from the contrast medium and cannot take up more iodine (radiolabeled) for the radionuclide scan. For this reason, iodine 123 imaging should not be performed for 6 to 8 weeks after an exogenous load of iodine. In this circumstance, the history and physical examination, as well as laboratory testing (for TRAB), must be relied on to make the correct diagnosis.

**Elevated human chorionic gonadotropin.** Iodine 123 nuclear imaging studies are forbidden during pregnancy. Therefore, all women of childbearing age should have a pregnancy test before undergoing radioisotope imaging. If thyrotoxicosis from hCG is suspected (eg, in cases of hydatidiform mole or choriocarcinoma), ultrasonography of the uterus should be done to rule out a viable pregnancy before pursuing radioisotope imaging.

**Treatment options** for the usual causes of hyperthyroidism (toxic nodular goiter or Graves disease) include radioactive iodine ablation (unless the patient was exposed to a recent cold iodine load), antithyroid drugs (methimazole or propylthiouracil), or surgical resection (partial or complete thyroidectomy).<sup>27</sup>

Patients with overt hyperthyroidism should be referred to an endocrinologist for a thorough evaluation and discussion of the diagnosis and the treatments that are available. Beta-blockers can be used to ameliorate the symptoms of thyrotoxicosis such as palpitations, anxiety, and tremor.

**Periodically reassess the thyroid function tests in patients with subclinical hyperthyroidism**

**If iodine 123 uptake is low**

A low (suppressed) TSH level, in conjunction with elevations of the free thyroid hormones and low uptake of iodine 123, is consistent with overt hyperthyroidism secondary to:

- Thyroiditis
- Ectopic hyperthyroidism due to T<sub>4</sub>-T<sub>3</sub> therapy, struma ovarii (very rare), or large deposits of functioning thyroid cancer metastases (very rare)
- Iodine-induced hyperthyroidism (Jod-Basedow effect)
- Amiodarone-induced thyrotoxicosis.<sup>27,28</sup>

**Thyroiditis**, ie, destruction or inflammation of thyroid tissue with subsequent release of preformed thyroid hormones into the circulation, results in thyrotoxicosis. The severity and duration of thyrotoxicosis depends not only on the size of the injured thyroid gland and the store of preformed thyroid hormones, but also on the extent and duration of the thyroid destruction and injury.

Subacute thyroiditis usually lasts several weeks to a few months, and typically follows a pattern of:

- Transient hyperthyroidism due to release of thyroid hormone stores
- A brief period of euthyroidism
- Hypothyroidism, as the store of preformed thyroid hormone is exhausted and thyroid inflammation and destruction subside, and then
- Recovery (usually, unless the thyroid is not capable of recovery), during which the TSH level rises in response to low levels of thyroid hormones in the circulation, and the recovering thyroid begins to resume thyroid hormone synthesis.<sup>28</sup>

There is a brief period during the hypothyroid phase of thyroiditis during which the TSH level remains low (or inappropriately normal), even though the free thyroid hormone levels are also low; this period is commonly called the “disequilibrium state” (FIGURE 2). This state is due to the slow recovery of the pituitary thyrotrophs as they escape tonic suppression by excess thyroid hormones.

The classic entity of de Quervain thyroiditis (subacute granulomatous thyroiditis) is painful, whereas other forms are painless (eg, autoimmune lymphocytic thyroiditis, postpartum, or related to cytokine [interferon] or

lithium therapy).<sup>28</sup> Other forms of thyroiditis, which may or may not be painful, include those induced by amiodarone, radiation, or trauma.

Regardless of the cause, watchful waiting is warranted while monitoring thyroid function tests to ensure that recovery takes place.<sup>28</sup> Beta-blockers are often used to decrease symptoms during the transient hyperthyroid state observed early in the course of thyroiditis.

**Ectopic hyperthyroidism.** Ingestion of exogenous T<sub>4</sub>, T<sub>3</sub>, or both can suppress thyroid function. This can occur with supratherapeutic T<sub>4</sub> and T<sub>3</sub> (usually for hypothyroidism) and also factitiously or in patients abusing the drugs to lose weight. A useful way to differentiate exogenous from endogenous causes of thyrotoxicosis is to measure serum thyroglobulin, which would be decreased in the former and elevated in the latter.

Ectopic production of T<sub>4</sub> and T<sub>3</sub> can occur, albeit rarely, as in cases of struma ovarii or in patients with large deposits of functioning thyroid cancer metastases.<sup>29-31</sup> Struma ovarii is a very rare ovarian teratoma (accounting for 1% of all ovarian tumors), and even when present it does not usually result in thyrotoxicosis.<sup>29,30</sup> However, the diagnosis should be considered in the appropriate clinical context, ie, in the setting of thyrotoxicosis and a pelvic mass; radioiodine uptake would be elevated in the pelvis in those cases.

Likewise, thyrotoxicosis secondary to functioning thyroid cancer metastases is also rare but should be considered in the right clinical context (iodine-avid tissue throughout the body noted on radioiodine whole-body imaging).

**Iodine-induced hyperthyroidism** develops in patients with underlying thyroid disease (toxic nodular goiter or Graves disease) and is caused by an exacerbation of autonomous (TSH-independent) thyroid function by an iodine load (eg, intravenous contrast medium that contains iodine, or amiodarone therapy [see below]).

**Amiodarone-induced thyrotoxicosis.** In various reports, the incidence of amiodarone-induced thyrotoxicosis ranged from 1% to 23%.<sup>32</sup> There are two types.

Type 1 is a form of iodine-induced hyperthyroidism. It can occur in patients with

**Patients with toxic nodular goiter are TRAB-negative and do not have ophthalmopathy**



autonomous thyroid function when they are exposed to amiodarone, which contains 37% iodine by weight.

Type 2 occurs in patients with no underlying thyroid disease and is probably a consequence of a drug-induced destructive thyroiditis. Mixed or indeterminate forms of amiodarone-induced thyrotoxicosis encompassing several features of both type 1 and type 2 may also be observed.<sup>20</sup>

The treatment varies by type: antithyroid drugs (thionamides) in type 1 and corticosteroids in type 2.<sup>20</sup> It can be difficult to discern between the two entities, and combination therapy with antithyroid drugs and prednisone may be needed. One of the drugs is then withdrawn, and the effect on the levels of free thyroid hormones is monitored. This helps determine which drug is working, pointing to the correct diagnosis and treatment.

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## CASE CONCLUDED

Our patient's thyroid function tests were repeated at the time of her endocrinology consult, 2 weeks after she was noted to have a low TSH in the setting of low free T<sub>4</sub>, which suggested central hypothyroidism. Her TSH level was now 3.5  $\mu$ U/mL, and her free T<sub>4</sub> level was 0.8. Thus, her low TSH in the setting of the low free T<sub>4</sub> noted 2 weeks earlier reflected a disequilibrium state, which occurs during the hypothyroid phase of thyroiditis (FIGURE 2).

Repeated measurements of her thyroid function tests verified complete recovery and resolution of her thyroiditis. No levothyroxine therapy was required, and no further investigation was performed.

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