

Thyroid Testing and Imaging

INTRODUCTION

This chapter reviews the most helpful tests for evaluating the thyroid patient. It also covers common thyroid imaging techniques. A brief discussion of thyroid physiology is included to help the reader better understand and evaluate thyroid test results.

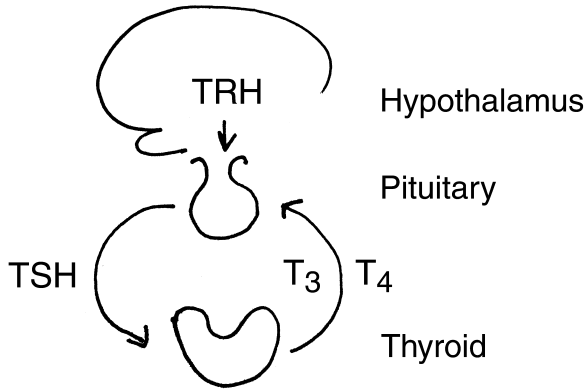
THYROID PHYSIOLOGY

This brief discussion of thyroid–pituitary physiology will help the reader interpret thyroid test results. The thyroid gland produces the thyroid hormones, triiodothyronine (T_3) and thyroxine (T_4) under the control of the pituitary gland's secretion of thyroid-stimulating hormone (TSH). TSH secretion is also controlled by thyroid-releasing hormone (TRH) from the hypothalamus. A classic endocrine feedback loop (Fig. 1) functions to keep thyroid hormone levels normal in a patient without thyroid or pituitary disease. Thus, a small increase in thyroid hormones in the blood is detected by the pituitary gland (and hypothalamus), and secretion of TSH is decreased. When thyroid hormone levels fall, pituitary TSH secretion rises. The thyroid synthesizes and secretes both T_4 and T_3 . However, much of the T_4 that is secreted is deiodinated to T_3 in the liver and other peripheral tissues. T_3 is the active hormone at the level of the peripheral cell nuclei and at the pituitary and hypothalamic level.

When the thyroid is unable to produce adequate thyroid hormones (hypothyroidism) because of a disease such as Hashimoto's thyroiditis, the pituitary gland senses the fall of thyroid levels in the blood and TSH secretion increases (Fig. 2). In contrast, when the thyroid produces excessive thyroid hormones (hyperthyroidism), as in Graves' disease, the TSH level falls below the normal range (Fig. 3). This feedback mechanism is the basis for biochemical testing of thyroid function.

LABORATORY EVALUATION OF THYROID FUNCTION

Thyroid testing has evolved over the past half century from the old basal metabolism test (BMR) to the current high-tech and very precise assays of



Thyroid - Pituitary - Hypothalamus
Relationship in a Normal Patient

TRH - Thyrotropin Releasing Hormone

TSH - Thyroid Stimulating Hormone

T₄ - Thyroxine

T₃ - Triiodothyronine

Fig. 1. Thyroid-pituitary-hypothalamus relationship in a normal patient.

TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone; T₃, triiodothyronine; T₄, thyroxine.

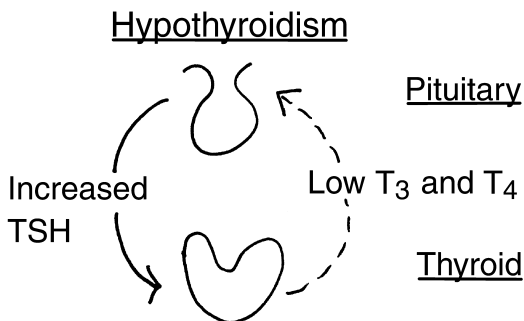


Fig. 2. Hypothyroidism.

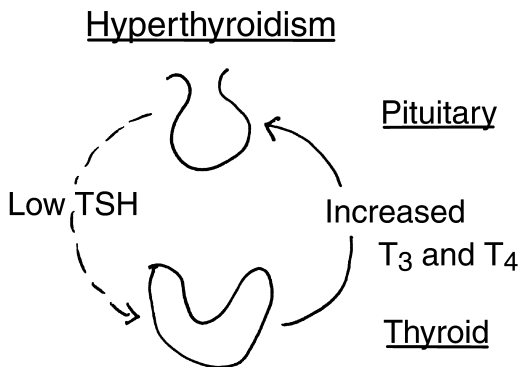


Fig. 3. Hyperthyroidism.

TSH, T₄, and T₃, as well as measurement of thyroid-binding proteins and antithyroid antibodies. Nuclear medicine tests, such as the radioiodine uptake (RAIU) and thyroid scan, which date back more than 50 years, are still useful. Fine-needle aspiration biopsy (FNAB), which has been available in the United States for more than 20 years, has become the first-line test in evaluation of thyroid nodules. Thyroid ultrasound is useful in specific situations in evaluating thyroid nodules. We have come a long way in evaluating the thyroid from the days of the BMR and the protein-bound iodine (PBI). This chapter discusses the most efficient and cost-effective use of these and other tests.

Thyroid-Stimulating Hormone

The TSH assay was one of the tests developed after Berson and Yalow developed the radioimmunoassay (RIA) technique to measure insulin for which they won the Nobel Prize[®]. It measures the pituitary hormone (TSH) that stimulates the thyroid to produce and secrete T₄ and T₃. However, the RIA measurement of TSH was not sensitive enough to separate a low-normal TSH from a low TSH. It was used on the other end of the scale to distinguish a normal from an elevated level. Thus, the test could be used to diagnose hypothyroidism (high TSH), but it was not useful in diagnosing hyperthyroidism. In about 1985, a new method for measuring TSH was developed. Immunoradiometric assay (IRMA) was 10 times as sensitive as RIA and could distinguish between a low-normal and a truly low TSH. Patients with hyperthyroidism were, as expected, found to have very low TSH levels. Now, with a single test one can diagnose both hypothyroidism and hyperthyroidism in most cases. This test was known as a *second-generation TSH* or sensitive TSH and was gradually adopted by clinical labs. Several years later, an even more sensitive TSH test, known as

third-generation TSH by immunochemiluminescent assay (ICMA), became available and has been adopted by many clinical labs.

When Should You Order TSH?

TSH has replaced T_4 as the first-line test in evaluation of thyroid function. It should be ordered when hypothyroidism or hyperthyroidism is suspected. It is also the best test for screening abnormal thyroid function. A normal TSH will, in most cases, rule out thyroid function abnormalities.

Evaluation of TSH Results

The normal range for TSH varies a bit between clinical laboratories, but is usually detailed on the lab report as between approx 0.4 and 5.5. Some researchers believe that the upper-normal level of around 5 is too high. A new “reference range” of 0.4 to 2.5 has been delineated, although this is not yet quoted as the “normal” range. The new reference range is still controversial (this issue is discussed further in Chapter 7). Most patients with overt hypothyroidism have a TSH of more than 10. Patients with TSH levels between 5.5 (or perhaps 2.5) and 10, with no findings of hypothyroidism and a normal T_4 , are diagnosed as having *subclinical hypothyroidism*. Treatment of these patients is controversial and is discussed in more detail later. Most patients with clinical hyperthyroidism have a TSH level that is very low, often unmeasurable by second- or third-generation TSH tests. Patients with a TSH below 0.4, normal T_3 and T_4 , and no clinical findings of hyperthyroidism are diagnosed as having *subclinical hyperthyroidism*.

When Are Other Thyroid Tests Needed?

If the patient has clinical findings of hypothyroidism or hyperthyroidism, a T_4 measurement, preferably a free thyroxine (FT_4), should be added. The combination of a low TSH and elevated FT_4 confirms a clinical diagnosis of hyperthyroidism. A low TSH may rarely indicate secondary hypothyroidism owing to hypopituitarism, but in this case, the FT_4 will also be low. A high TSH in combination with a low FT_4 will confirm a diagnosis of hypothyroidism. A high TSH may very rarely reflect a TSH-secreting pituitary tumor with hyperthyroidism, but in this case the FT_4 will also be elevated. The combination of a TSH and FT_4 will provide a diagnosis in most cases. Figure 4 provides a suggested algorithm for thyroid evaluation. Of course, the approach may vary in the individual patient.

Thyroxine

Like the TSH, the T_4 test has evolved over the past 50 years. Because T_4 has four iodine atoms per molecule, early tests relied on the measurement of iodine to estimate T_4 levels. Because more than 99% of T_4 is bound to protein in the blood, the PBI was developed to separate this fraction from the inorganic iodine in plasma. Inorganic iodine levels vary widely depending on iodine

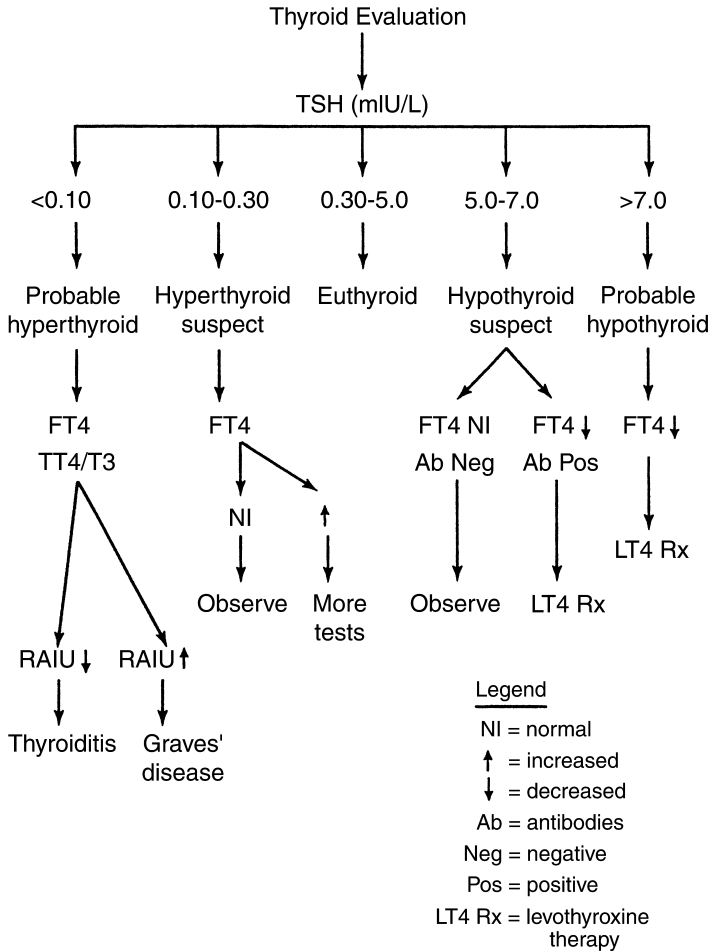


Fig. 4. Suggested algorithm for evaluation and management of thyroid disease when TSH is the initial diagnostic test. (From Kane LA, Gharib H. Thyroid testing: a clinical approach. In: Braverman LE, ed. Diseases of the Thyroid, 2nd ed. Humana Press, Totowa, NJ, 2003.)

intake. One major problem with this chemical test was the effect of large amounts of inorganic iodine, such as those found in cough syrups and cold medicines, in falsely elevating the PBI level. However, for a number of years, this was the best test available, and it was widely used. Modifications of this test based on iodine measurement were developed, but it could still be affected by inorganic iodine. A major improvement in T_4 measurement came with the RIA method. T_4 by RIA was not affected by inorganic iodine and was therefore more accurate. However, this method still measured total T_4 . Because more than 99% of T_4 is protein bound and inactive, this test could be falsely affected

by thyroid-binding protein (TBP) changes, as in pregnancy and in patients taking estrogen or birth control pills, which increase binding proteins.

The best current tests measure the free or active portion of T_4 either directly or indirectly. In most cases, these tests are not affected by changes in TBPs and give a true estimate of the clinically important portion of T_4 .

When Should You Order a T_4 ?

An FT_4 should usually be added to a TSH in any patient with clinical thyroid disease to confirm the diagnosis as just discussed. In most cases, a measured, FT_4 is best, although an estimate of T_4 can be obtained by ordering an FT_4 index. This is a calculated FT_4 based on a total T_4 measurement and a so-called T_3 uptake. The T_3 uptake has nothing to do with serum T_3 level, and is simply a laboratory's way of estimating TBPs.

How Do You Interpret the Result?

An elevated FT_4 along with a low TSH is usually diagnostic of hyperthyroidism. A low FT_4 along with an elevated TSH is usually diagnostic of hypothyroidism.

Triiodothyronine

T_3 , the other active thyroid hormone, was discovered more than 40 yr ago. Assays were developed for total T_3 and later for free triiodothyronine (FT_3). The total T_3 , like the total T_4 , may be affected by pregnancy and estrogens. Measurement of the free or active portion of the hormone by a good assay is usually more accurate.

When Should You Order a T_3 ?

The T_3 is useful in cases where the diagnosis is not clear after review of the TSH and T_4 results. An occasional patient with hyperthyroidism may have a low TSH, normal T_4 , and elevated T_3 , so-called T_3 toxicosis. It may also be useful in some patients who are undergoing treatment for thyroid dysfunction, and in acutely ill patients with so-called nonthyroidal illness. Nonthyroidal illness is discussed later in this chapter.

How Should You Interpret the Result?

An elevated FT_3 , in combination with a low TSH, confirms a diagnosis of hyperthyroidism even in the presence of a normal FT_4 .

Radioactive Iodine Uptake

The RAIU test measures the percentage of an orally administered dose of a radioactive form of iodide (usually iodine 123), which is taken up by the thyroid. The measurement is made with an external radiation detector at 4 or 6 and 24 h after administration of the tracer. The test has been available for more than

50 yr and was out of favor for a time after the improved serum tests became available. However, it has become useful again in the differential diagnosis of the etiology of hyperthyroidism.

How Should You Interpret the Result?

An elevated RAIU in the presence of clinical evidence for hyperthyroidism confirms a diagnosis of Graves' disease. A depressed (usually very low) uptake is compatible with hyperthyroidism resulting from thyroiditis.

Thyroid Antibodies

The etiology of the majority of cases of hyperthyroidism is Graves' disease, an autoimmune disease. Also, the large majority of cases of hypothyroidism are caused by Hashimoto's thyroiditis, another autoimmune disease. Thus, it is useful to measure thyroid antibodies in some patients. A brief discussion of several types of thyroid antibodies follows.

Thyroid Microsomal and Peroxidase Antibodies

A test for antithyroid microsomal antibodies has been available for many years. This test measures a cellular antibody that is often present in the blood of patients with Hashimoto's thyroiditis and may also be present in Graves' disease. More recently, a test for antibodies against thyroid peroxidase (TPO) has been developed. This enzyme is involved in the synthesis of T_4 in the thyroid cell. The TPO antibody test is an improvement over the microsomal antibody test and may also be positive in Hashimoto's thyroiditis and Graves' disease.

When Should You Order the TPO Antibody Test?

The TPO antibody test is useful in evaluating patients with hypothyroidism and diagnosing autoimmune thyroid disease. It is particularly useful in patients with subclinical hypothyroidism with mild TSH elevation because a positive test will confirm underlying thyroid disease. Because Hashimoto's thyroiditis often runs in families, it may be helpful to perform a TPO antibody test in relatives of patients with this diagnosis.

How Do You Evaluate the Result?

Most patients with Hashimoto's thyroiditis will have moderately or markedly elevated TPO levels, rather than borderline elevations. TPO elevation may help make the decision to treat mild or subclinical hypothyroidism, because patients with positive antibodies tend to progress from subclinical to clinical hypothyroidism over time.

TSH Receptor Antibodies

Antibodies against the TSH receptor on thyroid cells, such as thyroid-stimulating immunoglobulin (TSI), stimulate increased thyroid function and thyroid

hormone production resulting in hyperthyroidism. The TSI is often, but not always, positive in Graves' disease. In Graves' disease, the thyroid is no longer under the normal feedback control of pituitary TSH. Excessive stimulation by TSI results in hyperthyroidism.

When Should You Order a TSI Test?

The TSI may be useful in difficult or confusing cases of hyperthyroidism where the diagnosis is not clear. However, it is not needed in making the diagnosis of Graves' disease in most patients. Also, a negative test does not rule out Graves' disease.

THYROID IMAGING

Nuclear Thyroid Scan

This scan is often ordered along with the RAIU test. It has been used mainly in the diagnosis of thyroid nodules. The scan is done after administration of a radioactive tracer, either iodine 123 or technecium 99m. These tracers are concentrated in functioning thyroid tissue and can be imaged with a γ -camera. In a patient with a thyroid nodule, the report will determine whether the nodule is functioning (warm or hot) or nonfunctioning (cold). Functioning nodules are rarely cancerous, whereas nonfunctioning nodules may harbor a cancer. The problem with this test is that only about 5 to 10% of cold nodules are cancerous; the rest are benign. Thus, this test is sensitive but nonspecific.

When Should You Order a Nuclear Thyroid Scan?

The first-line test in diagnosis of thyroid nodules is FNAB. However, when FNAB results indicate the possibility of cancer but are not definite (follicular neoplasm), the finding of a hot nodule on a nuclear scan would make cancer very unlikely. Only about 10% of nodules are hot on scan. A cold nodule is not specific for cancer, and surgery might be needed to make a diagnosis. A nuclear scan may also be helpful in diagnosis of hyperthyroidism owing to a toxic nodule or toxic nodular goiter.

Thyroid Ultrasound

Thyroid ultrasound is often used in the evaluation of thyroid nodules. It will show whether a nodule is solid, cystic, or complex (having both solid and cystic components). The rationale for this test is that cancers are usually solid and most cysts are benign. The problem is that many nodules are complex and cystic carcinomas are occasionally seen. Thus, FNAB is still the most useful and specific study in evaluating thyroid nodules. Thyroid ultrasound is being used more frequently in guiding FNA and may also be used in accurately measuring the size of nodules and following them.

Fine-Needle Aspiration Biopsy

FNAB has been used in the United States in the evaluation of thyroid nodules for about 25 years. FNAB has become the first-line test in evaluation of thyroid nodules. The test is quite accurate in differentiating thyroid cancer (surgical) from benign thyroid nodules (usually nonsurgical) when performed by an experienced biopsier and interpreted by a cytopathologist experienced in this technique. Because only about 5% of nodules are cancerous and thyroid nodules are common, it is extremely useful and cost-effective to separate the patients needing surgery from the rest. In most large series, about 80% of diagnostic biopsies are benign, 5% are cancerous, and 15% are suspicious (follicular neoplasm). In the suspicious group, about 15% are cancerous and 85% are benign adenomas, but surgery is required to make the diagnosis. The false-negative rate is 2 to 5% when performed by an experienced biopsier and interpreted by an expert cytopathologist. Quantity not sufficient or nondiagnostic biopsies are in the range of 5 to 20%, depending on the experience of the biopsier and pathologist. If the nodule falls into the suspicious group, a nuclear scan may be helpful because hot nodules are rarely cancerous.

When Should FNAB Be Performed?

FNAB should be the first test performed after discovery of a thyroid nodule in most cases. It is sensitive and specific and is usually the best test to answer the critical question in the patient's mind: is it cancer?

Thyroid Function Tests in Nonthyroidal Illness

The previous discussion applies to thyroid testing in the outpatient setting where most thyroid testing is ordered. However, thyroid function tests are less reliable in seriously ill patients in the hospital, especially those in the intensive or coronary care units. The term "nonthyroidal illness" refers to patients who have abnormal thyroid tests but do not have thyroid disease or who may have transient thyroid disease secondary to the acute illness. This section attempts to briefly summarize this rather complex subject.

Thyroid tests are often ordered in acutely ill patients because of such findings as atrial fibrillation which suggests the possibility of hyperthyroidism, or lethargy and confusion which may in turn suggest hypothyroidism. Although the TSH alone is adequate to screen for thyroid disease in most outpatients, it is not sufficient in the intensive care unit. The TSH in this setting may be low for a number of reasons unrelated to thyroid disease, including drugs such as dopamine and steroids that are frequently used in acutely ill patients. The general recommendation is that thyroid tests should not be ordered in seriously ill patients unless there is a clinical reason, such as goiter or thyroid eye findings, to suspect thyroid disease, or if there is a history suggestive of thyroid disease.

If thyroid tests are indicated, a panel to include TSH, T_4 or FT_4 and T_3 or FT_3 should be ordered. The TSH should be done by third-generation technique that will measure TSH down to about 0.01. An undetectable TSH by this method along with an elevated T_3 would suggest hyperthyroidism. The findings in nonthyroidal illness might show a low but detectable TSH along with a low or low-normal T_3 . If possible, FT_3 and T_4 should be measured, rather than total T_3 and T_4 to avoid the effect of abnormalities in TBP.

TBP abnormalities are often seen in seriously ill patients. The thyroid hormones T_3 and T_4 are bound to thyroid-binding globulin, thyroid-binding prealbumin (or transthyretin) and albumin. Low levels of TBP are often seen in sick patients and will result in a decrease in total T_3 and T_4 . Patients who are on estrogens or who have liver disease may have elevated TBP and resulting increase in total T_3 and T_4 . Also, drugs such as androgens and nicotinic acid may decrease TBP and result in low total T_3 and T_4 . In patients on these drugs, the free hormone levels will usually be unaffected.

A complete discussion of nonthyroidal illness is beyond the scope of this book. However, the following points should be helpful:

- Remember that thyroid tests are more difficult to interpret in seriously ill patients in the hospital than in the outpatient setting.
- In general, do not order thyroid tests on hospital patients unless there is reason to suspect thyroid problems clinically.
- Order a complete panel rather than just a TSH in initial thyroid evaluation of sick hospital patients.
- Be aware that a low TSH may be secondary to the acute illness or medications, such as dopamine or steroids, rather than hyperthyroidism.
- Treatment with thyroid hormone is not helpful and may be harmful in patients with nonthyroidal illness who have abnormal thyroid tests but do not have hypothyroidism.

SUMMARY

Thyroid testing has come a long way in the past 50 years. The tests discussed here should help you sort out most thyroid problems. TSH is now the first-line test in evaluating patients suspected of having thyroid dysfunction and in thyroid screening. FNAB is the first-line test in evaluating most thyroid nodules. The other tests reviewed in this chapter are useful in specific patients. The problem of nonthyroidal illness in acutely ill patients is often difficult to sort out, but the points listed here should be helpful.

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