

American Thyroid Association Guidelines for Use of Laboratory Tests in Thyroid Disorders

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Selection of appropriate laboratory determinations will enable the clinician to diagnose thyroid dysfunction readily in the majority of patients. At the present time, estimation of free thyroxine and a "sensitive" thyrotropin assay are recommended as the principal laboratory tests for thyroid disease. A decrease in serum free thyroxine estimate and a raised level of serum thyrotropin confirm the diagnosis of hypothyroidism caused by thyroid gland failure. An increase in free thyroxine estimate combined with a serum sensitive thyrotropin level suppressed to less than 0.1 mU/L establishes the diagnosis of thyrotoxicosis. In sick patients, a normal or raised serum free thyroxine estimate together with a normal level of serum thyrotropin suggests that the patient has neither hypothyroidism nor thyrotoxicosis. Patients with severe illnesses, generally in the intensive care unit, and those treated with certain drugs, as well as individuals with unusual thyroid disorders, may present with confusing laboratory findings. An understanding of the regulation of the thyroid hormone system and/or judicious consultation with an endocrinologist should enable the clinician to diagnose thyroid disease, if present, in such patients. JAMA. 1990;263:1529-1532

CLINICAL investigations and commercial developments during the last decade have resulted in a large number of laboratory tests becoming available for diagnosis of thyroid dysfunction. To evaluate a patient for thyroid disease, the clinician must now select the most appropriate laboratory determinations from this bewildering array of tests. Many of these determinations have similar names and some lack diagnostic specificity. The American Thyroid Association has a continuing interest in clarifying and simplifying the nomenclature of these measurements; current guidelines for classification of tests and their nomenclature have been published recently.^[1] The purpose of the present report is to suggest to clinicians an approach to the laboratory diagnosis of the principal thyroid disorders. In consideration of the low frequency of undiagnosed thyroid disease in the adult population,^[2] the costs of various measurements, and the complexities in interpretation, our current view is that tests of thyroid function should not be part of multiphasic screening for patients who are not suspected to have thyroid disease, except in certain high-risk populations. Suspect populations include the newborn, for whom screening for congenital hypothyroidism is mandatory^[3]; individuals with a strong family history of thyroid disease; elderly patients^[4]; postpartum women 4 to 8 weeks after delivery, and patients with autoimmune diseases such as Addison's disease and type I diabetes mellitus. Rather, our premise is that clinicians will have a specific thyroid disease entity in mind when selection of tests is considered.

HYPOTHYROIDISM

In the ambulatory patient, the diagnosis of hypothyroidism is readily confirmed by finding a subnormal serum thyroxine (T₄) value. However, since T₄ is bound to specific serum-binding proteins, the serum T₄ concentration may be altered in the absence of thyroid disease in patients who have alterations in the concentration of serum-binding proteins, particularly T₄-binding globulin (**Table 1**). Frequently encountered clinical settings with increased serum protein binding of thyroid hormones include pregnancy and the use of oral contraceptives. Estimation of the free T₄ concentration is, therefore, recommended instead of total serum T₄ as the initial measurement of serum thyroid hormone concentration since the free T₄ estimate will be in the normal range in euthyroid persons despite increased or decreased binding proteins. As would be expected, significant decreases in levels of serum free T₄ are generally observed in hypothyroidism.

Table 1.-- Factors That Influence Thyroxine-Binding Globulin

Increase	Decrease
Oral contraceptives	Testosterone
Pregnancy	Corticosteroids
Estrogens	Severe illness
Infectious hepatitis	Cirrhosis
Chronic active hepatitis	Nephrotic syndrome
Neonatal state	Inherited
Acute intermittent porphyria	
Inherited	

A number of different methods for free T₄ assays are available for estimation of free T₄ concentrations. However, some of these free T₄ assays perform with variable accuracy in different clinical settings. For most purposes, a free T₄ estimate may be obtained by a free T₄ index, an analogue free T₄ assay, or any one of the other commonly used clinical chemical techniques. The free T₄ index is obtained via the total T₄ concentration and the thyroid hormone-binding ratio. The advantages and some pitfalls in these methods are discussed in a concurrent report (Ian D. Hay, MD, PhD, Monika F. Bayer, PhD, Michael M. Kaplan, MD, et al, unpublished data, October 1989). Throughout this report we will use the terms "free T₄ estimate" and "free T₄" interchangeably. Criteria for selection of free T₄ assays that will be appropriate for either ambulatory or inpatient settings are being discussed by the nomenclature committee of the American Thyroid Association (Ian D. Hay, MD, PhD, Monika F. Bayer, PhD, Michael M. Kaplan, MD, et al, unpublished data, October 1989). In this regard, clinicians should require that their chemical pathologists and other clinical pathologists who direct hospital or commercial laboratories understand the complexities and limitations of different free T₄ assays and employ appropriate criteria for selection of the appropriate free T₄ determination.

The cause of hypothyroidism in most cases is a disorder of the thyroid gland itself. Because of the negative feedback relationship between serum thyroid hormones and pituitary thyrotropin (thyroid-stimulating hormone [TSH]) secretion, a raised serum concentration of TSH occurs in most patients with hypothyroidism. These considerations suggest that clinicians should request determinations of both the serum free T₄ and serum TSH concentrations in patients who have a clinical syndrome that suggests hypothyroidism. The concomitant finding of a decrease in serum free T₄ and increase in serum TSH levels confirms the diagnosis of hypothyroidism caused by thyroid gland failure; an increase in the concentration of serum TSH together with a normal or lownormal serum free T₄ indicates that the patient may be at an early stage in the development of primary hypothyroidism. The etiology of thyroid failure may be established by a history of iodine 131 therapy, thyroidectomy, ingestion of antithyroid drugs, or a

high frequency of thyroid disease in the family. Significant titers of antithyroid microsomal antibodies indicate that the patient suffers from Hashimoto's thyroiditis or postpartum thyroid dysfunction. In contrast to the findings in primary hypothyroidism, a subnormal serum free T₄ concentration with a normal or subnormal serum TSH value suggests that the patient may have hypothyroidism secondary to a decrease in TSH secretion. This combination of results suggests a diagnosis of hypopituitarism and may warrant a detailed workup of the hypothalamic-pituitary axis by endocrinologic testing as well as radiographic procedures. Hypothyroidism caused by hypothalamic-pituitary disorders occurs infrequently in comparison with hypothyroidism that results from thyroid gland failure. Moreover, the decrease in pituitary TSH secretion is usually associated with deficiencies of other pituitary hormones. The laboratory diagnosis of hypothyroidism is more complex in sick patients who are hospitalized for various illnesses. Changes in thyroid hormone secretion, distribution, and metabolism, as well as subnormal concentrations of the plasma thyroxine-binding proteins, may occur in hospitalized patients. [5] [6] Furthermore, circulating inhibitors of the binding of T₄ and triiodothyronine (T₃) to the serum-binding proteins have also been reported. [7] [8] These manifold and complex changes in sick individuals may result in abnormal results for various tests of thyroid function even though the patient does not have a specific thyroid disorder. In general, the more severe the illness, the greater the degree of abnormality in findings from tests of thyroid function. Indeed, endocrine consultations are frequently requested for hospitalized patients to determine whether abnormalities in results of various tests of thyroid function are consistent with nonthyroidal illness alone or whether the patient may also have associated hypothyroidism. The abnormal circulating thyroid hormone or TSH concentrations in sick patients may be adaptations to the catabolic state; many of these changes also occur during fasting, and they revert to normal when the patient recovers. [9]

A useful approach for diagnosis of hypothyroidism in sick patients is to consider patients with mild to moderate illness separately from those with severe illness, who are often in the intensive care unit. In mild to moderate illness, the combined measurement of free T₄ and TSH levels should be sufficient to diagnose pre-existing hypothyroidism. In the absence of thyroid disease, the serum free T₄ estimate is generally normal or raised in mild to moderate illness, [10] and serum TSH is usually in the normal range. In such patients, the criteria for diagnosis of primary hypothyroidism or hypothyroidism caused by decreased TSH secretion are similar to those described above for ambulatory individuals. Measurements of serum T₃ serve no useful purpose, since serum T₃ concentration may be in the normal range in 20% to 30% of patients with hypothyroidism [11] and is subnormal in approximately 70% of hospitalized patients who prove not to have any intrinsic thyroid disease. [10]

The above guidelines for diagnosis of hypothyroidism become more difficult to apply as the patient's illness becomes more severe and/or chronic. Thus, serum T₄ concentration may be subnormal in more than 50% of patients in an intensive care unit, and free T₄ estimates by conventional assays, such as free T₄ index, are often decreased as well. [12] [13] One study has shown that a free T₄ determination by equilibrium dialysis will clearly distinguish euthyroid patients with hypothyroxinemia caused by severe illness from hypothyroid patients with serum T₄ levels that are decreased to a comparable degree. [14] Criteria for selection of the appropriate free T₄ assay to be used in the severely ill patient have recently been discussed (Ian D. Hay MD, PhD, Monika F. Bayer, PhD, Michael M. Kaplan, MD, et al, unpublished data, October 1989). [14] Thus, in patients with critical illness, simultaneous primary hypothyroidism should be diagnosed by finding a decrease in serum free T₄ and an elevation in serum TSH levels. A potential pitfall in this approach is the frequent use of dopamine and pharmacologic doses of corticosteroids in critically ill patient populations. These agents, commonly used in the intensive care unit, may suppress an elevated serum TSH concentration toward or into the normal range. [15] [16] Nevertheless, only a rare case of primary hypothyroidism does not exhibit significant elevation in serum TSH concentration.

Another possible pitfall in the diagnosis of primary hypothyroidism in the critically ill patient is the transiently raised concentration of serum TSH that is found in many euthyroid patients as they recover from severe illness.[9] [17] Values of serum TSH that are in the range previously considered diagnostic of primary hypothyroidism may occur in this setting; TSH generally returns to the normal range within a few days or weeks. Thus, the finding of low-normal or slightly decreased serum free T₄ concentrations in conjunction with increased concentrations of serum TSH when using conventional free T₄ assays is consistent with a diagnosis of either primary hypothyroidism or the euthyroid state in a patient who is recovering from critical illness. Since unrecognized primary hypothyroidism occurs in only about 1% of the adult population, most patients with these findings will be euthyroid. Clinical factors such as previous treatment for Graves' disease, thyroid surgery, significant titers of antithyroid microsomal antibodies, or findings on physical examination typical of hypothyroidism all would suggest that the elevation in serum TSH concentration is secondary to thyroid failure.

Only a rare patient with critical illness may have hypothyroidism that results from hypothalamic or pituitary disease associated with decreased TSH secretion; such patients will often have signs of hypogonadism and hypoadrenalism as well. The pituitary-adrenal axis should be evaluated in such patients by measuring serum cortisol, since an undiagnosed deficiency in cortisol could have grave clinical consequences in sick patients. The secondary hypothyroidism in these critically ill patients will be established by finding serum free T₄ in the hypothyroid range and serum TSH in the low-normal range or decreased. The apparently paradoxical finding of measurable serum "sensitive" TSH in some cases of secondary hypothyroidism apparently results from secretion of TSH that has reduced biologic activity. In the absence of hypothalamic or pituitary disease, a normal TSH value excludes primary thyroid disease, provided that the patient is not receiving dopamine.[16] The sensitive TSH assay is a new method to measure TSH and provides much greater sensitivity than the radioimmunoassay method (Ian D. Hay, MD, PhD, Monika F. Bayer, PhD, Michael M. Kaplan, MD, et al, unpublished data, October 1989).

TREATMENT OF HYPOTHYROIDISM

Laboratory measurements also serve as useful guides in the treatment of hypothyroid patients with levothyroxine sodium. The dosage and rapidity of treatment with levothyroxine depend on the clinical setting and are described elsewhere. The goal of therapy is to restore most patients to a euthyroid state and to normalize the serum T₄ and TSH concentrations. The recent availability of TSH assays that distinguish between normal TSH concentration and suppressed values such as occur in hyperthyroidism (see below) now enables the clinician to select a dose of levothyroxine that normalizes not only the clinical symptoms but also the serum T₄ and TSH concentrations. Monitoring the serum TSH level to ascertain that it remains above the lower limit of the normal range will prevent the potential risk of overtreatment with levothyroxine. In patients with hypothyroidism caused by hypothalamic-pituitary failure, alleviation of the clinical syndrome and restoration of serum T₄ to the normal range are the only criteria available for estimating the appropriate replacement dosage of levothyroxine.

HYPERTHYROIDISM

If the history and findings on physical examination suggest that the patient may have thyrotoxicosis, the diagnosis can be readily confirmed by the combined finding of an abnormally high concentration of serum thyroid hormones and, because of negative feedback inhibition on the pituitary, a subnormal serum TSH level, not previously measurable as such. Serum free T₄ concentration is increased in approximately 95% of ambulatory hyperthyroid patients; an occasional hyperthyroid patient may have increased serum T₃ alone (T₃-thyrotoxicosis). Because the serum concentrations of thyroid hormones are influenced by the concentration of serum binding proteins, clinicians should first order the determination of the level of free T₄ in conjunction with serum TSH level to establish the diagnosis. Major improvements in sensitivity of the serum TSH determination have occurred during the past several years. The original TSH radioimmunoassay method has been replaced with "sensitive" or "ultrasensitive" TSH assays. When the less sensitive TSH radioimmunoassay determinations were used, many euthyroid individuals had

undetectable serum TSH levels and could not be distinguished from hyperthyroid patients with suppressed TSH. Testing with thyrotropin-releasing hormone was frequently employed to separate these groups. The newer sensitive TSH assays clearly define a lower limit of the normal range for TSH, generally between 0.3 and 0.5 mU/L, varying according to the individual assay. The serum TSH level in hyperthyroid patients should be clearly subnormal; that is, less than 0.1 mU/L.[\[18\]](#) The combination of an increase in serum free T₄ level and a decrease in serum sensitive TSH level to less than 0.1 mU/L, therefore, suggests the diagnosis of hyperthyroidism. At the present time, we do not recommend sensitive TSH assays alone for evaluation of thyroid function. This is because of the relatively short-term clinical experience with these assays and the frequency of decreased values caused by drugs and possibly other factors in sick patients who do not have thyroid disease. An occasional hyperthyroid patient may have a decrease in the concentration of serum sensitive TSH but serum free T₄ concentration in the normal range. In these patients, a raised level of serum free T₃ will confirm the diagnosis of hyperthyroidism that results predominantly from increased T₃ secretion as well as provide a quantitative assessment of the severity of the thyrotoxic state.

Several other combinations of laboratory values may be confusing to the clinician and may warrant consultation with an endocrinologist. Thus, the concentration of serum sensitive TSH may be decreased in some individuals with serum free T₄ and serum free T₃ concentrations within the normal range. Similar to T₄, serum T₃ is also bound to serum proteins, and the free T₃ concentration may be a useful test to diagnose hyperthyroidism. In the absence of medications that suppress TSH secretion, these patients probably have mild thyrotoxicosis with minimal hypersecretion of thyroid hormone. Their abnormal thyroid state may be further established by a T₃-suppression test or by demonstration of a lack of response of serum TSH to thyrotropin-releasing hormone. Hyperthyroid patients with raised levels of serum free T₄ and free T₃ but with normal or increased levels of serum TSH may rarely be encountered. Their hyperthyroidism is caused by increased and autonomous TSH secretion, generally from a pituitary tumor.

Last, other euthyroid patients may have raised levels of serum T₄ and/or a raised serum free T₄ index but normal levels of serum sensitive TSH. Some of these individuals may have familial dysalbuminemic hyperthyroxinemia[\[19\]](#) or may have circulating anti-T₄ and/or anti-T₃ antibodies. Since these patients are clinically euthyroid, they should be encountered infrequently unless large populations are screened for thyroid dysfunction, which is not currently recommended as cost-effective strategy.

The diagnosis of hyperthyroidism is more complex in sick patients because of the broad array of influences of nonthyroidal illnesses on the serum thyroid hormone-binding proteins and thyroid hormone metabolism as well as the presence of circulating inhibitors of T₄ and T₃ binding to proteins. In hyperthyroid patients with mild illness, serum T₄ and T₃ levels will remain increased above the normal range; in moderate illness, the serum T₃ level may fall into the normal range, but the serum T₄ level generally remains elevated. However, in severe illness, serum T₄ and T₃ levels both may either decrease into the normal range or even become subnormal.[\[20\]](#) [\[21\]](#) [\[22\]](#) In all of these clinical settings, serum TSH concentration should be less than 0.1 mU/L in hyperthyroid patients who also have a nonthyroidal disease. However, the nonthyroidal illness itself or treatment with dopamine or with large doses of corticosteroids may also result in similar subnormal concentrations of serum TSH.[\[23\]](#) In such instances, serial monitoring of serum TSH levels and/or thyrotropin-releasing hormone testing may be required. Further testing may be required to establish the etiology of the thyrotoxic state after the diagnosis of thyrotoxicosis has been established by the approach discussed above. If the patient has a diffusely enlarged thyroid gland and exophthalmos, the etiology is almost certainly Graves' disease. The presence of one or more thyroid nodules in a patient with hyperthyroidism suggests a toxic adenoma or toxic multinodular goiter which can be confirmed simply by a thyroid scan with radioactive iodine. The concentration of radioactive iodine by the nodules and the absence of uptake in the remainder of the thyroid gland establish the diagnosis. Radioactive iodine should not be administered to pregnant women or nursing mothers. If one of these common etiologies of hyperthyroidism is not established, a radioactive

iodine uptake determination should be performed. The thyroidal radioiodine uptake is generally elevated in Graves' disease but is clearly subnormal in hyperthyroidism caused by subacute thyroiditis, "silent" (lymphocytic) thyroiditis, postpartum thyroid dysfunction, or thyrotoxicosis factitia. Finally, these forms of thyroiditis and thyrotoxicosis factitia can be distinguished from one another by determination of serum thyroglobulin. Since thyroglobulin is a protein that is produced uniquely by the thyroid gland, its serum concentration will be elevated in any form of thyrotoxicosis emanating from the thyroid gland, but will be decreased in thyrotoxicosis factitia.[24]

HYPOTHYROIDISM AND HYPERTHYROIDISM IN PREGNANCY

The diagnosis of hypothyroidism and hyperthyroidism during pregnancy employs the same laboratory tests and utilizes the same principles discussed above. Pregnancy is associated with an increase in levels of serum total T₄ and serum T₃ caused principally by a rise in the concentration of thyroxine-binding globulin, the predominant iodothyronine-binding protein in serum. Serum free T₄ concentrations should be normal in patients with increased thyroxine-binding globulin levels alone. Despite these changes, serum TSH concentration by sensitive assay is normal in pregnant women without thyroid disease.[25] Thus, hyperthyroidism in pregnant women can usually be diagnosed by an abnormally high level of serum free T₄ and suppressed serum TSH. Hypothyroidism can be documented by decreased serum free T₄ and increased serum TSH levels.

EFFECT OF DRUGS ON THYROID HORMONE MEASUREMENTS

Clinicians are frequently required to determine whether patients may have either hypothyroidism or hyperthyroidism at a time when they are taking medications that alter tests of thyroid function. The effects of several commonly prescribed drugs on thyroid function are therefore summarized. Phenytoin treatment of euthyroid patients results in a 30% to 40% decrease in serum T₄ and free T₄ levels and either normal or slightly decreased levels of serum T₃ and free T₃. [26] Serum TSH is in the normal range in phenytoin-treated patients. Treatment with carbamazepine and rifampin [27] also results in subnormal concentrations of serum free T₄.

A number of pharmacologic agents appear to act predominantly by decreasing the rate of production of T₃ from T₄ in the peripheral tissues. These agents include glucocorticoids [28] or propranolol hydrochloride [29] in high doses, oral cholecystographic radiopaque agents (iopanoic acid, sodium ipodate), [30] and amiodarone. [31] All result in decreased levels of serum T₃ and free T₃, normal or elevated levels of serum T₄ and free T₄, and, usually, normal levels of serum TSH. Large doses of glucocorticoids, however, may result in suppression of serum sensitive TSH and may also depress serum iodothyronine-binding proteins, resulting in decreased levels of serum T₄ and TSH. Last, dopamine, in doses that are employed to treat cardiovascular shock, generally results in decreased levels of serum sensitive TSH. 16 With the latter exceptions, however, the serum sensitive TSH value serves as a generally excellent guide for the detection of a hypothyroid or hyperthyroid state in patients receiving these medications.

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