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THYROID FUNCTION TESTS: A REVIEW

Biochemistry

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ABSTRACT

Thyroid function tests are one of the most common endocrine panels in general practice because a good understanding of when to order them, indications for treatment are important for the optimal treatment of thyroid dysfunction. Thyroid-stimulating hormone (TSH) should be the first test to be performed on any patient with suspected thyroid dysfunction and in follow-up of individuals on treatment. It is useful as a first-line test because even small changes in thyroid function are sufficient to cause a significant increase in TSH secretion. Thyroxine levels may be assessed in a patient with hyperthyroidism, to determine the severity of hyperthyroxinemia. Antithyroid peroxidase measurements should be considered while evaluating patients with subclinical hypothyroidism and can facilitate the identification of autoimmune thyroiditis during the evaluation of nodular thyroid disease. The measurement of TSH receptor antibody must be considered when confirmation of Graves' disease is needed and radioactive iodine uptake cannot be done.

KEYWORDS

Hypothyroidism; Hyperthyroidism; Thyroiditis; Thyroxine; Thyroid stimulating hormone; Thyroglobulin (TG).

INTRODUCTION

Thyroid dysfunction is a common condition encountered in clinical practice the world over and India is no exception.[1]Clinically, this condition may present with a wide range of symptoms.[2-3]This makes thyroid function tests (TFTs), one of the most ubiquitous endocrine panels in general practice. However, the interpretation of these can be rather challenging and can cause considerable bewilderment, more often than not. A good understanding of TFTs, when to order them, how to interpret their results as well as when to treat is, therefore, key to optimal treatment of thyroid dysfunction.[4]The patient may present with obvious features of hypothyroidism or hyperthyroidism. In these conditions thyroid hormone (TH) concentration only confirm the diagnosis. However, in many patients the signs or symptoms can be nonspecific, vague or mild, especially in females.[5]The prevalence of treated hypothyroidism is increasing in both the United Kingdom and the United States [6-7]. Furthermore, the global prevalence of undiagnosed thyroid dysfunction, at least in the developed world, is falling, probably due to a combination of iodine supplementation in iodine deficient areas, widespread and frequent thyroid function assessment, and lower thresholds to commence treatment[8-9].Approximately,1–3%ofthepopulationhas hypothyroidism in iodine-replete areas, with much higher prevalence in older persons and in women [9-10]. Current guidelines for the diagnosis and management of thyroid dysfunction focus primarily on the measurement of TSH, as the most sensitive and specific marker of systemic thyroid status, with test results interpreted according to defined reference ranges [9-10]. This article aims to review the indications for interpretation of thyroid function tests.

THYROID PHYSIOLOGY AND PATHOPHISIOLOGY

The hypothalamus produces thyrotropin-releasing hormone (TRH) which acts on the pituitary gland.[11] This stimulates the pituitary to release thyroid-stimulating hormone (TSH), which in turn stimulates the thyroid gland to secrete thyroxine (T4) and triiodothyronine (T3)[12,13] [Figure 1].TSH demonstrates a negative feedback on the hypothalamus, while T4 and T3 have the same on the pituitary gland as well as the hypothalamus.[14]

Primary hypothyroidism and hyperthyroidism

In primary hyperthyroidism, the increased secretion of thyroid hormones causes a negative feedback, resulting in a suppression of the levels of serum TSH **[Figure 1].**

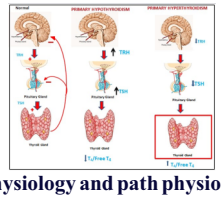

Figure 1: Thyroid physiology and path physiology.

Secondary hypothyroidism and hyperthyroidism

The abnormality is at the level of the hypothalamus or the pituitary gland, in these disorders. Surgery on sellar or on suprasellar masses are an important cause of secondary hypothyroidism.15 It is essential to remember that, even though the levels of T4 are low, those of TSH may be well within the normal range. Such a patient would require thyroid hormone replacement. The apparently normal value of TSH is, in fact, an inappropriately low value. In these patients, the levels of T4 have to be monitored so that the dose of thyroxine may be adjusted accordingly [Figure 1].

THYROID FUNCTION TESTS

Thyroid-Stimulating Hormone (TSH)

Thyroid-stimulating hormone (TSH) is a glycoprotein hormone secreted by the anterior pituitary. Serum TSH normally exhibits a diurnal variation with a peak shortly after midnight and a nadir in the late afternoon. At the peak of this variation the TSH can be double the value at the nadir.[16] TSH is now firmly established as the first-line thyroid function test to assess thyroid status for most clinical conditions.[17] The diagnostic superiority of TSH measurement arises principally from the physiological inverse log-linear relationship between circulating TSH and free T4 (FT4) concentrations. An abnormal TSH is the first abnormality to appear in thyroid disease, where other thyroid tests can be normal. Using TSH as a single criterion has been shown to accurately classify the thyroid state of a patient in over 95% of cases.[18]

Table 1: Typical thyroid function test results in hypothyroidism

S.NO.	CAUSES	TSH	Thyroid function tests	
			T3	T4
1	Ioidine deficiency disorder	Increase	Decrease	Decrease
2	Hasimoto's thyroiditis	Increase	Normal Decrease	Normal Decrease
3	Pituitary abnormality	decrease	Decrease	Decrease
4	Non-thyroidal illness	Variable	Normal Decrease	Decrease

Table 2: Typical thyroid function test results in hypothyroidism

S.NO	CAUSES	TSH	Thyroid function tests	
			T3	T4
1	Grave's disease	Decrease	Increase	Increase
2	Hasimoto's Thyroiditis (early stage)	Decrease	Increase	Increase

TSH alone can only be used to assess thyroid status when the pituitary-thyroid axis is stable. Non-thyroidal illness (NTI), pituitary disease

and various drugs can all affect the axis and cause discrepancies between TSH levels, thyroid hormone levels and the clinical state. Glucocorticoids, dopamine and octreotide can all suppress TSH secretion. [19] Many clinicians prefer thyroid stimulating hormone (TSH) as the initial screening test for suspected patient with thyroid disease as it is the key hormone for diagnosing hyperthyroidism and hypothyroidism.[20] The reason behind TSH being the screening tests is because, it is central to the negative feedback mechanism and tiny variation in thyroid function causes dramatic changes in TSH secretion. With the use of most advanced third generation chemiluminescent TSH assay it is now possible to detect both significant raised and decreased TSH levels and are capable to detect as low as <0.1mU/L of TSH.[21]

TSH may be decreased in the following conditions:

- Primary hyperthyroidism
- Pituitary/hypothalamic disease
- Prolonged thyrotroph cell suppression after recent hyper thyroidism in euthyroid or hypothyroid patient
- Old age
- Drugs, e.g., glucocorticoids, dopamine
- Non thyroidal illnesses
- Combination of pulsatile TSH secretion and analytical precision limits

TSH may be elevated in the following conditions:

- Primary hypothyroidism
- Pituitary adenoma (TSH producing)
- Pituitary resistance to thyroidhormone (TSH, unreliable)
- Generalized thyroid hormone resistance
- Thyrotoxicosis from overly rapid correction of severe hypothyroidism with use of parenteral thyroxine
- Old age
- Drugs, e.g., amiodarone
- Recovery phase after severe systemic illness
- Combination of pulsatile TSH secretion and analytical precision limits
- Antibody in patient serum against antibody in TSH assay, causing analytical artifact

Automated immunoassays are preferred in the measurement of thyroid function tests due to high specificity and sensitivity toward a large panel of heterogeneous molecules with short turnaround time. However immunoassays are prone to different types of interferences that can affect clinical decisions[22]

THYROTROPIN RELEASING HORMONE (TRH)

Prior to the availability of sensitive TSH assays, thyrotropin releasing hormone (TRH) stimulation tests were relied upon for confirming and assessing the degree of suppression in suspected hyperthyroidism. Typically, this stimulation test involves determining basal TSH levels and levels 15 to 30 minutes after an intravenous bolus of TRH. Normally, TSH would rise into the concentration range measurable with less sensitive TSH assays that could provide useful information from the profile of increase even if they were not sensitive enough to measure baseline values. Third generation assays do not have this limitation and thus TRH stimulation is generally not required when third generation assays are used to assess degree of suppression. TRH-stimulation testing however continues to be useful for the differential diagnosis of secondary (pituitary disorder) and tertiary (hypothalamic disorder) hypothyroidism. Patients with these conditions appear to have physiologically inactive TSH in their circulation that is recognized by TSH assays to a degree such that they may yield misleading, "euthyroid" TSH results. The TRH-stimulation test produces a very characteristic sluggish rise in TSH values.

- Helpful in diagnosis in patients with confusing TFTs. In primary hyperthyroidism TSH are low and TRH administration induces little or no change in TSH levels.
- In hypothyroidism due to end organ failure, administration of TRH produces a prompt increase in TSH.
- In hypothyroidism due to pituitary disease administration of TRH does not produce an increase in TSH.
- In hypothyroidism due to hypothalamic disease, administration of TRH produces a delayed (60-120 minutes, rather than 15-30 minutes) increase in TSH.

TOTAL T4 (TT4) AND FREE T4 (FT4)

T4 assays complement TSH assays, and are used to confirm a thyroid disorder when this is suggested by an abnormal TSH result. Furthermore, T4 assays may become the front- line assays in conditions that are known to possibly compromise the reliability of TSH results. Several months may be required for the dynamics of the regulatory mechanism (along the hypothalamic-pituitary-thyroid axis) to fully equilibrate after a treatment regimen is initiated or significantly altered; during this time TSH results may be misleading. Secondary (hypothalamic disorder) and tertiary (pituitary disorder) hypothyroidism are other conditions in which TSH results may be misleading, and the differential diagnosis is likely to rely on T4 (Free T4) results complemented by the characteristic profile of TSH results obtained during a TRH-stimulation testing procedure. (See TSH).

The total T4 test measures the concentration of thyroxine in the serum, including both the protein bound and free hormone. The total (but not the free) hormone concentration is dependent on the concentration of thyroid transport proteins, specifically thyroid binding globulin (TBG), albumin, and thyroid binding prealbumin (transthyretin). Thus any conditions that affects levels of thyroid binding proteins will affect the total (but not the free) T4 hormone levels. For example, estrogens and acute liver disease will increase thyroid binding, while androgens, steroids, chronic liver disease and severe illness can decrease it. Also, while TT4 is usually elevated in hyperthyroidism, it misses 5% of cases that are due to triiodothyronine (T3) toxicosis (see below).

The free T4 (FT4) assay measures the concentration of free thyroxine, the only biologically active fraction, in the serum (about 0.05% of the total T4). The free thyroxine is not affected by changes in concentrations of binding proteins such as TBG and thyroid binding prealbumin. Thus such conditions as pregnancy, or estrogen and androgen therapy do not affect the FT4.Thus the FT4 assays generally are considered to provide the more reliable indication of true thyroid status because only the free hormone is physiologically active. In developing hypothyroidism, T4 (free T4) is the more sensitive indicator of developing disease than is T3 (Free T3), and is therefore preferred for confirming hypothyroidism that has already been suggested by an elevated TSH result.

TT4 and FT4 are not always reliable indicators of thyroid disease. For example, a substantial proportion of seriously ill patients will have abnormal thyroid function in the absence of true thyroid disease, due to "sick euthyroid syndrome." Also, screening with TT4 or FT4 will generate many false-positive results in healthy populations. And, because TT4 and FT4 are normal by definition in subclinical thyroid dysfunction, they are not useful as screening tests for this condition.

TOTAL AND FREE TRIIODOTHYRONINE (T3)

The total T3 test measures the concentration of triiodothyronine in the serum. The T3 is increased in almost all cases of hyperthyroidism and usually goes up before the T4 does. Thus T3 levels are a more sensitive indicator of hyperthyroidism than the total T4, and T3 levels are therefore preferred for confirming hyperthyroidism that has already been suggested by a suppressed TSH result. T3 assays are also useful for the differential diagnosis of T3 thyrotoxicosis, a variant of hyperthyroidism that manifests itself with abnormally elevated T3 and suppressed TSH levels, while T4 levels remain within euthyroid (normal) limits. In hypothyroidism the T3 is often normal even when the T4 is low. The T3 is decreased during acute illness and starvation, and is affected by several medications including Inderal, steroids and amiodarone. This test measures both bound and free hormone. And only the free hormone is biologically active. Since free T3 accounts for only about 0.5% of the total T3, measurement of free hormone is generally considered to provide the more reliable indication of true thyroid status. As noted above for T4 levels, anything which effects thyroid binding globulin (TBG), or albumin will effect the total T3 levels.

RESIN THYROID UPTAKE (T-UPTAKE)

These assays have been variously referred to as T3-uptake, T4-uptake and thyroid-uptake tests, depending on the assay design. All are used in exactly the same manner and for the same purpose, not as stand-alone assays, but in combination with total T4 or total T3 assays. Matched T-uptake and total T4 results are used to calculate a free thyroxine index (FT4I or FT3I). The FT4I serves as an indirect estimate of free T4 levels, and were heavily relied upon historically, particularly before direct free T4 assays became available. The resin T3/T4 uptake is used

to assess the binding capacity of the serum for thyroid hormone. This is used to help determine if the total T4 is reflecting the free T4, or if abnormalities in binding capacity are responsible for changes in T4 values and thus this test is only useful in conjunction with Total T4 or Total T3. In the Resin T3 Uptake test, labeled hormone is added to the patient's serum. If there is an increase in binding capacity, more labeled hormone will be bound to the binding proteins and thus less will be left free in the serum. The free labeled hormone in the serum is measured and usually reported as a percent of the total labeled hormone added. If a patient has a high total T4,it may be due to overproduction of thyroid hormone (Hyperthyroidism) or to an excess of one of the thyroid binding proteins, usually thyroid binding globulin (TBG). If the high Total T4 is secondary to high TBG, the Resin T3 will be low, otherwise it will be normal or elevated. Another way of putting this is that if the Total T4 or Total T3 deviates from normal in one direction and the Resin T3 uptake deviates in the opposite direction, then the abnormality is due to changes in binding capacity, otherwise it is secondary to a true change in thyroid function (i.e. Hyper- or Hypothyroidism). For example, if the binding capacity is increased because of high estrogens, the free labeled hormone will be decreased and the Resin T3 uptake will be decreased.

REVERSE T3 (RT3)

Reverse T3 (RT3) is formed when T4 is deiodinated at the 5 position. RT3 has little or no biological activity and serves as a disposal path for T4. During periods of starvation or severe physical stress, the level of RT3 increases while the level of T3 decreases. In hypothyroidism both RT3 and T3 levels decrease. Thus RT3 can be used to help distinguish between hypothyroidism and the changes in thyroid function associated with acute illness, such as euthyroid sick syndrome.

ANTITHYROID ANTIBODIES (AUTOANTIBODIES)

Autoantibodies of clinical interest in thyroid disease include thyroid-stimulating antibodies (TSAb), TSH receptor-binding inhibitory immunoglobulins (TBII), antithyro- globulin antibodies (Anti-Tg Ab) and the antithyroid peroxidase antibody (Anti-TPO Ab). Of these, anti-TPO Ab has emerged as the most generally useful marker for the diagnosis and management of autoimmune thyroid disease.

The Anti-TPO Ab was historically referred to as the antimicrosomal antibody. The thyroid peroxidase enzyme (responsible for iodinating tyrosine residues in the thyroglobulin molecule) was subsequently identified as the major microsomal component recognized by these autoantibodies. New, improved assays, designed in the wake of this insight, have been rapidly replacing the older antimicrosomal antibody assays.

Anti-TPO Abs mediate antibody-dependent thyroid cell destruction; levels correlate with the active phase of the disease. Measurement of this autoantibody is useful for resolving the diagnostic dilemma presented by the apparent inconsistency between elevated TSH and normal free T4 results. Given abnormally elevated TSH and euthyroid T4 results, a positive anti-TPO Ab test provides strong evidence for early, subclinical autoimmune disease. This assay is also used to monitor response to immunotherapy, to identify at-risk individuals (with family history of thyroid disease), and as a predictor of postpartum thyroiditis. Approximately 10 percent of asymptomatic individuals have elevated levels of Anti-TPO Ab that may suggest a predisposition to thyroid autoimmune disease. Elevated levels are found in virtually all cases of Hashimoto's thyroiditis and in approximately 85 percent of Graves' disease cases.

Historically, Anti-TG Ab determinations were used in tandem with antimicrosomal Ab determinations to maximize the probability of a positive result in patients with autoimmune disease. Although the prevalence of Anti-TG Abs in thyroid autoimmune disease is significant (85 percent and 30 percent in Hashimito's thyroiditis and Graves' disease, respectively), it is much lower than the prevalence of the Anti-TPO Abs. The diagnostic information provided by Anti-TPO assays is rarely improved upon by the addition of an Anti-TG determination. The growing trend is to adopt the anti-TPO Ab test as the front-line test for autoimmune disease and no longer to routinely use the anti-TG assay routinely for this purpose. Because anti-TG Abs constitutes interference in thyroglobulin (TG) assays, another major use of the anti-TG test is to screen samples that have been submitted for

THYROGLOBULIN DETERMINATIONS

Thyroid-stimulating antibodies (TSAb) are present in more than 90% of Grave's Disease. TSH receptor-binding inhibitory immuno-globulins (TBII) are present in atrophic form of Hashimoto's Disease, maternal serum of pregnant women (predictive of congenital hypothyroidism) and myxedema.

Thyroid Binding Globulin (TBG)

TBG remains an esoteric thyroid function test that is useful for the differential diagnosis of patients presenting with significantly abnormal levels of total thyroid hormone levels but no other clinical signs or symptoms of thyroid disease. Depending on genetic determinants, the patient's health status (including pregnancy), and medication, TBG levels can vary widely from very elevated to very low. Total hormone levels also adjust accordingly, to maintain free thyroid hormone levels within the euthyroid range. In certain situations, the knowledge that grossly abnormal thyroid hormone levels are not the consequence of a thyroid disorder may be very reassuring. Although not widely used, there has been some interest in the ratio of total T4 to TBG (thyroid hormone bonding ratio) as an index of free T4 levels.

THYROGLOBULIN (TG)

TG is only produced by thyroid tissue and this makes it an extremely specific marker for functioning thyroid tissue. The complete absence of TG provides strong evidence for the absence of any functioning tissue. Thus tests for remaining thyroid tissue are particularly important for monitoring thyroid cancer patients for residual, metastasized, and recurring thyroid tissue after the thyroid has been completely removed. Historically, the only procedure available for this purpose has been the total body scan. An appropriately sensitive TG assay offers a powerful complementary procedure that may in certain situations reduce reliance on the far more invasive total body scans. Anti-Tg antibodies interfere in the TG assay, and TG results may therefore not be reported for serum samples that are positive for these antibodies.

SUBCLINICAL THYROID DISEASE

Subclinical thyroid disease is a term applied to patients with no or minimal thyroid-related symptoms with abnormal laboratory values, and is diagnosed more frequently now with the use of TSH as a screening test. Subclinical hyperthyroidism is defined as a low serum TSH concentration with normal serum FT4 and FT3 concentrations. This pattern of biochemistry may reflect mild thyroid hormone excess but may also reflect hypothalamic or pituitary disease, NTI or ingestion of drugs that inhibit TSH secretion. Subclinical hypothyroidism is defined as an increased TSH with normal FT4 and FT3 levels. [23]

NON-THYROIDAL ILLNESS

A condition characterized by abnormal thyroid function tests encountered in patients with acute or chronic systemic illnesses is described as non-thyroidal illness (NTI).[24]After the onset of NTI as early as 24 hours changes in T3 and TSH is noted in patients with chronic liver disease, chronic kidney disease, after surgery, myocardial infarction, malignancy, sepsis, burns, malignancy and even individual with poor nutrition. [25, 26] In NTI, TFT pattern is abnormal which may further evolve or change as the underlying primary disease does. fT4 and fT3 become low or low-normal while TSH remains normal or even low. [27,28] If total thyroid hormone concentrations are measured, even in mild NTI, there is marked reduction in T4 and T3 level. This is due to reduced thyroid binding protein concentration which leads to decreased in serum thyroid hormone binding capacity in ill patient. In case with acute, major psychiatric illness, T4 is elevated with normal TSH value which in some patients come to normal level in a short interval of time (<2 weeks).[29]

During recovery from intercurrent illness, TH and TSH concentrations return to normal. However, in some patients TSH may remain elevated for a short period of time which precedes the elevation in T4 and T3 level, suggesting that it is required for the restoration of euthyroidism.[30] It is important to be aware of this transient phenomenon in order to avoid inappropriate diagnosis and treatment. Thus TFT should be avoided in ill patients until or unless it is required for the management of the patients. These patients are usually considered euthyroid, but it has been debated whether these changes during illness are representative of an associated pathology requiring thyroid hormone replacement therapy or are indeed an adaptive response to stress to decrease metabolic rate, which in turn may be beneficial to the sick patient.[31]

CONCLUSION

The fundamental testing to be done in any patient with suspected thyroid dysfunction is the determination of the level of serum TSH. Whereas the measurement of T4 levels is recommended in patients with hyperthyroidism, the same is seldom required for T3. The assessment of free thyroid hormones is recommended in situations where thyroid binding globulin levels may be altered, such as oral contraceptive use or in nephrotic syndrome. In a pregnant woman, overtreatment may be more beneficial than undertreatment. The levels of serum TSH during the first trimester must never be allowed to go beyond 2.5 μIU/L and should be monitored every 6 weeks. The clinical presentation remains the most important component of the deciding process in terms of the initiation of therapy. When in doubt – supposing the results from biochemical evaluation are not in line with the clinical status of the patient – it is imperative that treatment is based on clinical assessment after confirming with the laboratory for any possible analytical error.

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