Thyroid disease: thyroid function tests and interpretation

This article aims to review the indications for thyroid function tests and their interpretation.

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Diseases of the thyroid are among the most prevalent of medical conditions, especially in women, but the symptoms can be relatively nonspecific or mild. For this reason, clinicians have been placing increased reliance on the laboratory for assistance in the diagnosis of thyroid disorders. In the 1950s, only one thyroid test was available, the protein-bound iodine estimate of the serum total thyroxine (T4) concentration which showed a poor sensitivity and specificity for thyroid disease. Technological advances have increased the number of thyroid-related tests available and have progressively improved the specificity, reproducibility and sensitivity of thyroid testing methods, allowing an accurate diagnosis of thyroid status to be made in the majority of cases. However, sensitivity, specificity and standardisation issues still result in substantial between-method variability for many of these tests, and analytical interference is still a common problem. This article aims to review the indications for thyroid function tests and their interpretation.

Thyroid-stimulating hormone

Thyroid-stimulating hormone (TSH) is a glycoprotein hormone secreted by the anterior pituitary. Because of variations in the polysaccharide side chains, TSH occurs in various isoforms, with a range of biological activities. 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.[1] TSH values can be expected to vary by as much as 20% between measurements without any change occurring in thyroid status.[2]

TSH is now firmly established as the first-line thyroid function test to assess thyroid status for most clinical conditions.[3] 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.[4]

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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.[5] The discrepancy between the serum half-life of TSH (1 hour) and that of T4 (1 week) can lead to discordant TSH/FT4 values when thyroid status is in flux. Abnormal TSH levels can persist for weeks or even months after initiation of treatment for thyroid disorders. Measurement of the TSH level is indicated for patients with symptoms suggestive of thyroid dysfunction, reduced bone mineral density, dyslipidaemia, depression, or atrial fibrillation.

Over the past few years the TSH reference interval has become controversial. The lower TSH reference limit has been shown to be approximately 0.3 mIU/l irrespective of the population or the method used. In contrast, the setting of the TSH upper reference limit has become contentious with estimates ranging from 2.1 mIU/l to 7.5 mIU/l.[6] Multiple factors influence the calculation of the TSH upper reference including population demographics like sex, ethnicity, iodine intake, body mass index, smoking status and age, as well as the failure to exclude the presence of subclinical thyroid disease. Complicating this is the fact that current TSH assays differ in specificity

for recognising different circulating TSH isoforms and that this can give rise to a 1.0 mIU/l difference in TSH values reported by different assays. The TSH reference interval also varies with age and stage of pregnancy.

Thyroid hormones

T4 is the principal hormone secreted by the thyroid gland. It is a prohormone with minimal biological activity, but gets de-iodinated in the peripheral tissues to the active hormone tri-iodothyronine (T3). Thyroid-binding proteins (thyroxin-binding globulin, transthyretin, and albumin) bind almost all of the available thyroid hormones in serum. However, it is the minute free fraction of hormone (0.02% for T4 and 0.2% for T3) that is responsible for the biological activity of thyroid hormones. FT4 assays have increasingly become accepted as a superior indicator of thyroid status because they should, theoretically, be independent of changes in thyroid-binding proteins, which influence total hormone measurements. However, the validity of these assays has been challenged. Despite constant improvements, current free hormone immunoassays still appear sensitive to alterations in serum albumin and abnormal binding proteins as well as certain drugs, high free fatty acid levels and other substances which compete for binding sites on thyroid-binding proteins. Free hormone levels are less reliable measures of thyroid function than are TSH assays because they are more susceptible to factors that can adversely affect test accuracy. FT4 is indicated as a second-line test, used to investigate situations in which TSH abnormalities are found, or where TSH measurements are known to be unreliable.[6]

The only real indication for free T3 (FT3) measurement, other than monitoring the occasional patient on T3 replacement, is if FT4 is not above the reference range in a patient with a low serum TSH. In this case an elevated FT3 indicates a diagnosis of T3-toxicosis. T3-toxicosis is not a disease entity but a description of a biochemical profile typically observed in mild cases of toxic nodular hyperthyroidism and early in the course of Graves' disease.[7] If the TSH is elevated, measurement of FT3 provides little additional information.[8]

Free thyroid hormone immunoassays are notoriously prone to interference. Phenytoin, carbamazepine, furosemide and non-steroidal anti-inflammatory drugs compete with thyroid hormone in binding to serum binding proteins and may increase FT4.[9] *In vivo* administration of heparin liberates free fatty acids, which displace thyroid hormones from their binding proteins and also increase FT4. FT4 reference intervals vary widely between methods, and interpretation requires method-specific ranges. The reference interval also varies with age, stage of pregnancy and geographic location. FT4 and FT3 have an intra-individual biological variation of 10% and 8% respectively, but unlike TSH show no diurnal variation.[2]

Interpretation of thyroid function tests

In overt primary hyperthyroidism TSH is nearly always below 0.10 mIU/l and the FT4 is above the reference range. In overt primary hypothyroidism plasma TSH is always increased with a suppressed FT4.[3] However, interpretation of thyroid function tests when there is discordance of results can be a little more challenging. Table 1 lists some causes of discrepant results, and the more common ones are discussed below.

In most clinical situations involving discordant FT4 and TSH results, the TSH test usually yields the most diagnostically reliable result, provided that the patient is not receiving medications that directly inhibit TSH secretion, and there are no conditions affecting the pituitary-thyroid axis.[6] Repeat testing may be particularly helpful in determining the cause of abnormal FT4 results after taking a careful history to screen for drug interferences. Repeat values will trend back towards normal over time if the abnormality was transient, while the abnormality will persist if it is due to underlying thyroid dysfunction.

It should be recognised that the intrinsic log-linear TSH-FT4 relationship dictates that modest changes in TSH would not be expected to be associated with changes in FT4 values outside the normal reference range, and in fact normal FT4 values with slightly abnormal TSH values are the definition of subclinical disease.

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. The prevalence is 1 - 2% in the general population, but higher in people older than 60 years of age, and

Table 1. Causes of discordant thyroid function test results

Raised TSH with a normal or raised FT4	Low TSH with a normal or low FT4
Subclinical hyperthyroidism	Subclinical hyperthyroidism
Recent treatment of hypothyroidism	Recent treatment of hyperthyroidism
NTI (recovery phase)	T3 toxicosis
Drugs	Drugs (steroids, dopamine)
Interfering antibody	NTI
Resistance to thyroid hormone	Pituitary disease
Central hyperthyroidism	
Normal TSH with a raised FT4	**Normal TSH with a low FT4**
Intermittent T4 therapy	NTI
Interfering antibodies	Recent treatment of hyperthyroidism
Familial dysalbuminaemic hyperthyroxinaemia	Interfering antibody
Central hyperthyroidism	Pituitary disease

in women.[10] Patients with subclinical hyperthyroidism that cannot be explained by NTI or drug therapy should have repeat thyroid function testing after 3 - 6 months. More frequent testing may be appropriate if the subject is elderly or has underlying vascular disease.

Subclinical hypothyroidism is defined as an increased TSH with normal FT4 and FT3 levels. The prevalence is 4 - 10% in the general population, and is higher in women and the elderly, affecting up to 20% of women over 60 years old.[10] Subjects with subclinical hypothyroidism should have the pattern confirmed within 3 - 6 months to exclude transient causes of elevated TSH. The measurement of thyroid antibodies is indicated as it helps to define the risk of developing overt hypothyroidism. Management of subclinical disease is controversial and is discussed elsewhere.[11]

Non-thyroidal illness

The NTI syndrome describes a condition characterised by abnormal thyroid function tests encountered in patients with acute or chronic systemic illnesses. This condition may affect 60 - 70% of critically ill patients and occurs in both organic and psychiatric disease.[12] 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. A decrease in T3 is the most common finding in these patients, occurring in even the mildest forms of NTI.[12] In the majority of these sick patients TSH will be normal and thus provides the best guide of thyroid status. However, in some patients, TSH concentrations may be suppressed in the acute phase and on recovery TSH concentrations may rise transiently into the hypothyroid range. Similarly, a high, normal or low T4 may also occur in sick patients. In hospitalised patients, an elevated TSH is as likely to be due to recovery from NTI as primary hypothyroidism, and a TSH <0.10 mIU/l is at least twice as likely to be due to NTI as hyperthyroidism.[13] It is for this reason that performing thyroid function tests is not advised for ill patients unless specifically indicated.

Inappropriate TSH

This is a biochemical diagnosis in which elevation in circulating FT4 and/or FT3 is associated with an inappropriately normal or elevated serum TSH concentration. If this biochemical picture is observed then an assay artefact or laboratory error should be considered first.[3] Common explanations are binding protein abnormalities leading to apparent elevation of FT4 (e.g. familial dysalbuminaemic hyperthyroxinaemia) or antibody interference with measurements of FT4, FT3 or TSH. Other causes of inappropriate TSH include TSH-secreting pituitary tumour (TSHoma) or a syndrome of thyroid hormone resistance. Both of these are rare and should be referred for further management. Syndromes of thyroid hormone resistance can often be confirmed by family history and thyroid testing of family members. In central hypo- or hyperthyroidism it is worth noting that abnormal TSH isoforms are often secreted. These isoforms may have increased or decreased biological activity but may react unpredictably with TSH assays. Thus the TSH result will not give an accurate prediction of TSH activity.

Antibody interference

Interfering antibodies are intrinsic antibodies that can cause unpredictable results on thyroid testing. They can be heterophile (nonspecific) antibodies, human anti-animal antibodies or autoantibodies to TSH, T4 or T3. Although assays are designed to minimise such interferences, problems still occur in between 0.03% and 3% of all samples.[14, 15] It is most commonly first suspected by the physician who sees a gross discordance between the clinical presentation of the patient and the laboratory test result. When antibody interference is suspected, the first step should be to re-measure both TSH and FT4 using a different manufacturer's platform.

Conclusion

Although in most cases interpretation of thyroid function tests with TSH and FT4 is straightforward, unusual conditions can generate unusual patterns of thyroid function tests which can be difficult to interpret. However, with the appropriate follow-up tests, and with consultation with the laboratory, most of these cases can be resolved easily.

References available at cmej.org.za

In a nutshell

- Thyroid diseases are common and in most cases the interpretation of thyroid function tests is straightforward.
- TSH should be used as the first-line thyroid function test to assess thyroid hormone status.
- TSH testing should not be used in the presence of NTI, pituitary disease or TSH-suppressing drugs.
- FT4 is indicated as a second-line test, used to investigate situations in which TSH abnormalities are found, or where TSH measurements are known to be unreliable.
- TSH and FT4 reference intervals are not universal. Use the appropriate interval provided by the laboratory.
- FT3 should be used only to diagnose T3-toxicosis or for monitoring T3 replacement therapy.
- When interpreting discordant FT4 and TSH results, the TSH test usually yields the most diagnostically reliable result.
- Subclinical thyroid disease is common and is characterised by an abnormal TSH with a normal FT4.
- In cases of discordant results, especially if there is clinical discordance, consider analytical inference.
- Rare causes of inappropriate TSH include TSH-secreting pituitary tumours and syndromes of thyroid hormone resistance.