Thyroid function tests

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Summary

Thyroid disorders can be difficult to detect clinically, but thyroid function tests can assist in making a diagnosis. Measuring thyroid stimulating hormone is the first step. If it is abnormal, free thyroxine should be measured. A raised concentration of thyroid stimulating hormone with a low concentration of free thyroxine suggests hypothyroidism. A low concentration of thyroid stimulating hormone with a high concentration of free thyroxine suggests hyperthyroidism. Measuring thyroid autoantibodies may help establish the cause of the dysfunction. Different assays can give different results, and tests of thyroid function may be affected by drugs and intercurrent illness.

Key words: thyroxine, triiodothyronine, thyroid stimulating hormone.

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Introduction

The thyroid gland secretes thyroxine (T_4) and triiodothyronine (T_3). These hormones are essential for normal growth, development and metabolic function.

Altered thyroid function is common. For example, the prevalence of hypothyroidism may be up to nearly 10% of the general population.[1] As thyroid disorders may not present with classical clinical signs, it is essential to have accurate assays of thyroid function to assist in the diagnosis.

Thyroid physiology (Fig. 1)

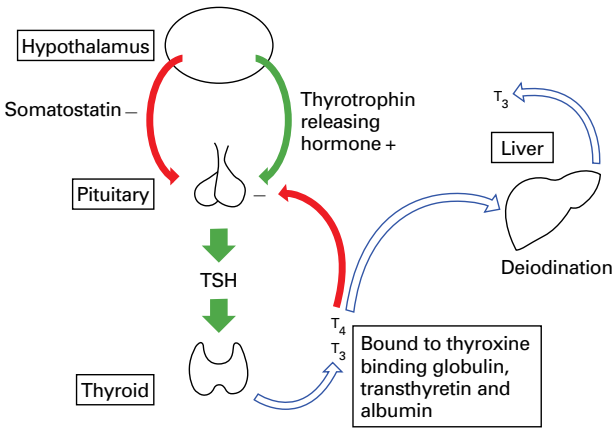
The thyroid gland actively transports diet-derived iodide from the blood by means of a cell membrane iodide pump called the sodium-iodide symporter. Iodide then combines with tyrosines in thyroglobulin, mediated by thyroperoxidase, to form T_4 (4 iodine atoms) or T_3 (3 iodine atoms). The uptake of iodide and the release of T_4 and T_3 are enhanced by thyroid stimulating hormone (TSH) which is secreted by the pituitary gland.

About 90% of thyroid hormone released is T_4 and 10% is T_3. In some hyperthyroid states the ratio of T_3 to T_4 is higher. Both hormones are co-secreted with thyroglobulin and circulate in blood bound to thyroid hormone binding proteins (thyroid binding globulin, transthyretin and albumin). A very small unbound ('free') fraction is available for uptake by cells. Much of the T_3 in the blood is generated by the liver after enzymatic removal of an iodine atom from T_4.

TSH secretion is mainly regulated by circulating T_4 (which is deiodinated to T_3 in the pituitary) and to a lesser extent by circulating T_3. There is a classical negative feedback loop between T_4 and TSH. This is log-linear (log TSH is inversely proportional to free T_4), which means that small changes in free T_4 cause large

Fig. 1

Pituitary-thyroid physiology



The hypothalamic hormones thyrotrophin releasing hormone and somatostatin stimulate or block secretion of thyroid stimulating hormone (TSH). TSH stimulates iodide uptake by the thyroid and synthesis of the thyroid hormones thyroxine (T_4) and triiodothyronine (T_3). T_4 and T_3 circulate bound to the thyroid hormone binding proteins (thyroxine binding globulin, transthyretin and albumin). A very small free fraction of thyroid hormone is available for cellular action. T_4 is deiodinated in liver and other tissues to form the more biologically active T_3. T_4 is also deiodinated in the pituitary to T_3 which inhibits TSH secretion.

inverse changes in TSH concentrations. TSH secretion is also regulated by the hypothalamic hormones thyrotrophin releasing hormone (stimulating) and somatostatin (inhibiting).

Blood tests relevant to thyroid disease

TSH is the hormone which is usually tested. It is the only test funded by the Medicare Benefits Scheme to screen for thyroid disease when there is no history of thyroid problems.

Thyroid stimulating hormone

TSH is a sensitive marker of thyroid function because it is influenced by small changes in free T_4 concentrations. A low TSH usually indicates hyperthyroidism whereas raised TSH usually means hypothyroidism. Over the years the lowest concentration of TSH which can be detected by assays has progressively fallen, allowing better separation of normal and hyperthyroid states.

Thyroid hormone assays

Only very small fractions of thyroid hormones are not bound to protein. These free thyroid hormones are the physiologically important thyroid hormones in blood. Modern immunoassays that estimate free hormone concentrations are widely available.

Changes in serum albumin concentrations, abnormal binding proteins, free fatty acids and drugs such as heparin, frusemide and phenytoin may interfere with these assays. Most laboratories now use chemiluminescent methods that are more (but not completely) resistant to such interference. When results do not fit into a recognised pattern the laboratory should be consulted to identify such interferences.

Thyroid-related autoantibodies

If a person has altered thyroid function, testing for thyroid antibodies helps to determine if they have an autoimmune condition.

Thyroperoxidase autoantibodies

Thyroperoxidase antibodies are also known as thyroid microsomal antibodies. They are present in autoimmune thyroid disease, but there is debate about whether low levels are always pathological. Unfortunately, there are significant differences between laboratories when the same sera are studied, and lower detection limits are variable. Assay sensitivities and reference ranges can therefore vary quite widely.

Thyroperoxidase antibodies can cause hypothyroidism in at least two ways. Firstly they can block thyroperoxidase thereby inhibiting T_4 and T_3 synthesis and secondly through antibody-dependent cell cytotoxicity and thyroid inflammation. Low concentrations may not be associated with evidence of thyroid dysfunction, but the incidence of raised TSH increases as antibody levels rise. The prevalence of positive antibody levels and mild hypothyroidism increases with age.

The concentration of thyroperoxidase antibodies may fluctuate in patients with autoimmune thyroid disease. This has no clinical significance and repeated measurements are not recommended. Maternal thyroperoxidase antibodies cross the placenta, but their effects on fetal thyroid function are unclear.

Thyroglobulin autoantibodies

Thyroglobulin autoantibodies are also a marker of autoimmune thyroid disease, but are less common than thyroperoxidase antibodies. Thyroglobulin autoantibodies do not inhibit thyroperoxidase or mediate antibody-dependent cell cytotoxicity and are therefore markers rather than mediators of autoimmune thyroid disease. There are considerable variations in sensitivity and reference ranges between assays. Other autoimmune diseases can also increase the concentration of thyroglobulin autoantibodies.

TSH receptor autoantibodies

TSH receptor autoantibodies may stimulate or less commonly block the TSH receptor. Stimulating antibodies cause Graves' disease and probably also cause the associated ophthalmopathy. Blocking antibodies can cause hypothyroidism. The assay of TSH receptor autoantibodies done in clinical laboratories cannot distinguish between stimulating or blocking antibodies. This is not usually relevant as clinical hyperthyroidism would suggest that the dominant antibody is stimulatory.

Measuring TSH receptor autoantibodies can be useful if the cause of hyperthyroidism is not apparent. However, initial hopes that remission of Graves' could be predicted by falling autoantibody levels have not been supported by most studies.

Measurements of TSH receptor autoantibodies do have an important role in managing pregnant women with Graves' disease. High concentrations of maternal TSH receptor autoantibodies can predict fetal and neonatal hyperthyroidism. It is important to recognise that TSH receptor autoantibodies do not always fall after successful treatment, so pregnant women with a previous history of Graves' disease should be screened for TSH receptor autoantibodies.

Thyroglobulin

Thyroglobulin, a large glycoprotein, represents about 80% of the wet weight of the thyroid and is co-secreted with thyroid hormone. Concentrations are high in patients with raised TSH concentrations or nodular goitres, but it is not clinically useful to measure thyroglobulin in these situations.

Most papillary and follicular carcinomas synthesise and secrete thyroglobulin, but raised thyroglobulin levels are not a reliable indicator or screening test for thyroid malignancy. Thyroglobulin concentration becomes a useful marker of remaining or recurrent cancer in patients who have had a total thyroidectomy and remnant ablation with radioiodine for papillary and follicular carcinoma.

Unfortunately, up to 20% of patients with differentiated thyroid cancer have thyroglobulin autoantibodies that interfere with the thyroglobulin assay, leading to underestimation of thyroglobulin concentration. Thyroglobulin autoantibodies should therefore be measured, with a sensitive assay, on all thyroglobulin samples.

Reference ranges

As most commercial assays do not physically measure the analyte, results given are always an approximation of actual levels. Each assay, even for the same analyte, will therefore give slightly different results because of intrinsic variations in the reagents used and the effects of interfering illnesses and substances. Free T_3 levels are the most variable between assay methods.

Reference ranges are altered by ethnicity, age and iodine intake. In Australia these factors are probably not clinically significant. Different ranges also apply in pregnancy, neonates and very young children.

Reference ranges are defined as those into which 95% of a normal population fall. (Accordingly 2.5% of normals will have higher and 2.5% will have lower results than the reference range.) Each assay must therefore be interpreted in terms of its own reference range. The practical implications of this are that blood test results from different laboratories may not be directly comparable and their interpretation requires examination of the reference ranges.

Reference ranges change in pregnancy. In early pregnancy chorionic gonadotrophin is secreted by the placenta in large amounts. This is structurally similar to TSH (but is not measured by the TSH assay) and stimulates the maternal thyroid. This leads to increased maternal thyroid hormone secretion and a reduced maternal TSH. Occasionally women develop mild hyperthyroidism in the first trimester, especially if they have hyperemesis.

Detecting and confirming thyroid dysfunction (Table 1)

The inverse log-linear relationship between free T_4 and TSH means that TSH concentrations are sensitive indicators of thyroid dysfunction. A raised TSH suggests hypothyroidism[2] while a low TSH suggests hyperthyroidism. There are other causes of low TSH concentrations, notably hypothalamic-pituitary disease, but this is very uncommon in the general population. The finding of an abnormal TSH should lead to measurement of free T_4 levels.

Interpretation of thyroid function tests may be particularly difficult if the patient is systemically ill. Starvation or severe illness can be associated with dysregulation of TSH secretion and reduced deiodination of T_4 to T_3 (the 'sick euthyroid' syndrome). Low TSH and T_3 levels are typical and can cause diagnostic confusion.

Very occasionally a raised TSH with a normal free T_4 relates to interference in the TSH assay. Very rarely, thyroid hormone resistance or a pituitary TSH-secreting adenoma is associated with a mildly raised TSH in the presence of a raised free T_4.

Treatment with amiodarone is often associated with abnormal thyroid function tests. The most common finding is a raised TSH caused by inhibition of pituitary T_4 to T_3 conversion, but true hypothyroidism and hyperthyroidism can occur. Diagnosis and management may be complex and require expert advice.

Hyperthyroidism

A low TSH and raised free T_4 indicate hyperthyroidism and should lead to consideration of causation and treatment. The majority of younger patients will have Graves' disease, but older patients are more likely to have nodular thyroid disease.

Table 1

Common results of thyroid function tests

Thyroid stimulating hormone	Free thyroxine	Free tri-iodothyronine	Thyroperoxidase and thyroglobulin autoantibodies	Comment
↔	↔	↔	↔	Normal
↑	↓	↓	↑	Primary hypothyroidism (Hashimoto's)
↑	↔	↔	↑	Subclinical hypothyroidism (Hashimoto's)
↓	↑	↑	↑	Hyperthyroidism (consider Graves', measure TSH receptor autoantibodies)
↓	↔	↔	↔	Subclinical hyperthyroidism (consider nodular thyroid disease)
↔↓	↓	↓	↔	Consider pituitary disease
↓	↔	↑	variable	T_3 toxicosis

↔ normal ↑ raised ↓ reduced

Transitory hyperthyroidism can be seen in patients with viral thyroiditis. Most have had a recent upper respiratory tract infection and present with neck tenderness and pain, which may be referred to the ear.

Some patients have a low TSH but normal free T_4. Measurement of free T_3 can then be helpful as some patients will have T_3 toxicosis caused by overproduction of T_3. If T_3 is not raised a repeat measurement of T_4 and TSH is warranted. This may show normal values, but a persistently low TSH with a normal free T_4 suggests autonomous thyroid function and a diagnosis of 'subclinical hyperthyroidism', which is usually associated with a nodular goitre (or, unusually, hypothalamic-pituitary disease). Subclinical hyperthyroidism in the elderly is associated with an increased risk of atrial fibrillation, stroke and osteoporosis.

Hypothyroidism

A raised TSH and a low free T_4 indicate primary hypothyroidism, almost always due to autoimmune thyroid disease but sometimes due to previous surgery or radioiodine administration. The incidence of raised TSH and thyroid antibody levels and hypothyroidism increases with age and is significantly more common in women.

It is not uncommon to find a raised TSH but normal free T_4. In most cases this suggests autoimmune thyroid disease. This subclinical hypothyroidism is more likely to progress to overt hypothyroidism when higher levels of TSH and thyroid autoantibodies are present.

Asymptomatic patients with a raised TSH and normal free T_4 require regular monitoring, especially if they are elderly or have high levels of antithyroperoxidase autoantibodies. Every six months is probably sufficient.

There is considerable debate about the normal upper limit of the TSH reference range. The high background prevalence of autoimmune thyroid disease as well as the age, iodine status, smoking prevalence and ethnicity of the 'normal' population has raised the 'normal' upper limit. In people without these factors the upper limit is probably 2.5 mIU/L. While mildly raised TSH levels rarely require treatment, a concentration above 4.0 mIU/L and the presence of thyroid antibodies is predictive of eventual hypothyroidism and indicates that these patients need to be followed up.[3]

Adjusting thyroxine treatment

Replacement thyroxine in hypothyroid patients should be adjusted to maintain TSH at about 2 mIU/L. It takes about six weeks for a change in thyroxine dose to achieve stable concentrations of free T_4. Changes to the dose of thyroxine, and tests of thyroid function, should not be done more frequently, unless clinically indicated. It is not uncommon for patients who are less than optimally compliant with recommended thyroxine treatment to take several tablets before a doctor's visit. This may be associated with a raised TSH, but normal free T_4.

Many patients with a history of differentiated thyroid cancer are advised to take suppressive doses of thyroxine. Guidelines[4] suggest that with persistent disease TSH should be kept below 0.1 mIU/L. Patients who presented with high-risk disease, but who are clinically free of disease, are advised to maintain TSH between 0.1 and 0.5 mIU/L for 5–10 years. Advice from commercial pathology laboratories that thyroxine doses be reduced in these patients should be resisted.

Adjusting treatment for hyperthyroidism

TSH may remain suppressed for weeks or even months after a patient starts antithyroid medications. It is useful to monitor free T_4 and free T_3 every 6–12 weeks to judge the adequacy of treatment. A rise in TSH indicates overtreatment. Patients with severe hyperthyroidism may need more frequent monitoring.

Conclusion

Thyroid dysfunction is common in the general population and TSH measurements provide a sensitive method for detection. An abnormal TSH requires further investigation, including at least measurement of free T_4. Interpretation of the results of thyroid function tests is facilitated by an understanding of thyroid hormone physiology, especially the normal inverse relationship between free T_4 and TSH concentrations. Variations in assay performance mean that it may be helpful to consistently use the same laboratory for an individual patient. An understanding of the effects of severe illness and medications on test results is also important.

References

1. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. Arch Intern Med 2000;160:526-34.
2. Ladenson PW, Singer PA, Ain KB, Bagchi N, Bigos ST, Levy EG, et al. American Thyroid Association guidelines for detection of thyroid dysfunction. Arch Intern Med 2000;160:1573-5.
3. Walsh JP, Bremner AP, Feddema P, Leedman PJ, Brown SJ, O'Leary P. Thyrotropin and thyroid antibodies as predictors of hypothyroidism: a 13-year, longitudinal study of a community-based cohort using current immunoassay techniques. J Clin Endocrinol Metab 2010;95:1095-104.
4. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19:1167-214.

Conflict of interest: none declared