

Investigating Thyroid Function



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Acknowledgement

bpac^{nz} would like to thank Associate Professor Patrick Manning, Dr Cam Kyle and Dr Mike Croxson for their help and advice on the development of this resource.

October 2005
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All information is intended for use by competent health care professionals and should be utilised in conjunction with pertinent clinical data.

Why focus on thyroid function tests?

- TSH and FT4 are commonly ordered tests.
- TSH and FT4 (and FT3) are frequently ordered simultaneously as “thyroid function tests”.
- The choice of “thyroid function test” has changed over the last 10-15 years; previously FT4 has been the most popular test, now TSH is favoured.
- It is now possible to make recommendations based on current understanding.

bpac^{nz} recommends

1. Asymptomatic patients are not screened for thyroid dysfunction.
2. TSH is used as the sole test of thyroid function in most situations.

Why do we make these recommendations?

1. Patients with no symptoms of thyroid disease and no obvious risk factors have a low likelihood of thyroid disease.
2. In most situations, TSH is the more sensitive indicator of thyroid status. If further thyroid function tests are indicated they can be subsequently added by the laboratory, or the GP usually without the need to retest the patient.

Despite the development of highly sensitive laboratory tests, clinical assessment and judgement remain paramount¹

Initial testing for thyroid dysfunction should be based on clinical suspicion. When more of the common signs and symptoms of thyroid disease are present, there is increased prevalence of disease. In 1997, Bandolier revisited a 1978 study² which emphasised the importance of clinical examination and history as the most significant factors when deciding to request thyroid function tests.

KEY POINT

Signs and symptoms provide the best indication to request thyroid tests

In the study, 500 consecutive patients were assessed for thyroid dysfunction. They were classified as high, intermediate or low suspicion of thyroid dysfunction on the basis of presenting signs and symptoms.

In the patients classified as high suspicion, 78% were subsequently identified as having a thyroid disorder. In the group with intermediate suspicion, 2.9% had a thyroid disorder, and in the group with a low degree of suspicion, 0.45% were found to have a thyroid disorder.

Signs and symptoms of thyroid disease

	Hypothyroidism	Hyperthyroidism
High Suspicion	Goitre Delayed reflexes	Goitre Thyroid bruit Lid lag Proptosis
Intermediate Suspicion	Fatigue Weight gain/difficulty losing weight Cold intolerance Dry, rough, pale skin Constipation Family history Hoarseness	Fatigue Weight loss despite increased appetite Heat intolerance/sweating Fine tremor Family history Increased bowel movements Fast heart rate/palpitations Staring gaze
Low Suspicion Non specific symptoms	Coarse, dry hair Hair loss Muscle cramps/muscle aches Depression Irritability Memory loss Abnormal menstrual cycles Decreased libido	Nervousness Insomnia Breathlessness Light or absent menstrual periods Weight loss Muscle weakness Warm moist skin Hair loss

Screening patients at increased risk?

Although some patients are at increased risk of thyroid dysfunction, screening is not recommended unless there are signs and symptoms of thyroid disease. Groups at increased risk include postpartum women, and women over the age of 50. However, in some groups symptoms can be non-specific and confusing. In the elderly for instance, hypothyroidism may be confused with Alzheimer's disease; while in post partum women, the symptoms of hypothyroidism may be confused with symptoms of post natal depression.

Patients who are likely to be at increased risk of thyroid dysfunction: ^{5,6}

- Patients with other autoimmune diseases (e.g. type 1 diabetes, coeliac disease)
- Patients with dyslipidaemia (high cholesterol and/or high triglyceride)
- Those taking some drugs, e.g. amiodarone, lithium, interferon
- Past history of neck surgery or irradiation
- Suspicious thyroid symptoms postpartum or a previous episode of postpartum thyroiditis
- Chronic cardiac failure, coronary artery disease, arrhythmias, pulse >90/min, hypertension
- Menstrual disturbance or unexplained infertility
- Some genetic conditions (e.g. Down, Turner syndromes)

Screening asymptomatic patients

Routine or opportunistic screening of asymptomatic patients is not recommended. The return of positive results is low and there is controversy around the value of treatment in apparently healthy people whose only indication of thyroid dysfunction is an abnormal test result.³ While there have been several studies performed to assess the benefit of treatment in asymptomatic patients, the results are conflicting.⁴ Until there is clear resolution supporting the benefits of treating asymptomatic patients, screening and case finding is not recommended.

KEY POINT

Routine screening of asymptomatic individuals is not recommended

Which test should be used?

In most situations use TSH as the sole test of thyroid function. It is the most sensitive test of thyroid function and adding other tests is only of value in specific circumstances.

KEY POINT

TSH is the best test for the routine assessment of thyroid function

In normal patients, when the TSH is within the reference range, there is a 99% likelihood that the FT4 will also be within the reference range. Furthermore, in a recent study of 1392 patients,⁷ in which both TSH and FT4 were performed, both test results were found to be consistent with euthyroidism, hypothyroidism, or hyperthyroidism in 96% of cases. Another 3.8% of patients were found to have results consistent with subclinical thyroid dysfunction. The study determined that using TSH alone as an initial test is adequate for testing patients on 99.6% of occasions.

When is it inappropriate to test only TSH?

Central (secondary) hypothyroidism - This is the most significant condition in which an incorrect diagnosis of euthyroidism could be made, based on TSH alone.⁸ When a patient is suspected of having pituitary failure both TSH and FT4 should be requested, as typically the patient has a normal TSH with a decreased FT4. Symptoms which may alert you to this rare, but significant condition include: menstrual disturbance, loss of sex drive, galactorrhoea, unexplained weight gain, skin changes, headaches/visual disturbances, and symptoms of hypoadrenalism, such as lethargy and dizziness.

Non compliance with replacement therapy - In hypothyroid patients suspected of intermittent use or non-adherence with their thyroxine replacement regimen, both TSH and FT4 should be used for monitoring. Non-adherent patients may exhibit discordant serum TSH and FT4 values (eg high TSH/high FT4) because of disequilibrium between TSH and FT4.

Early stages of therapy - During the first 2 months of treatment for hypo- or hyperthyroidism, patients will have unstable thyroid status because TSH will not have reached equilibrium. Early in thyroid replacement therapy, FT4 is the more reliable test, but testing should preferably be deferred for 2 months after a dose alteration. With anti-thyroid therapy, both TSH and FT4 are required for early monitoring (see later section)

Acutely ill patients - TSH is altered independent of thyroid status. As a result, testing should only be performed when it is likely to have an effect on acute management.

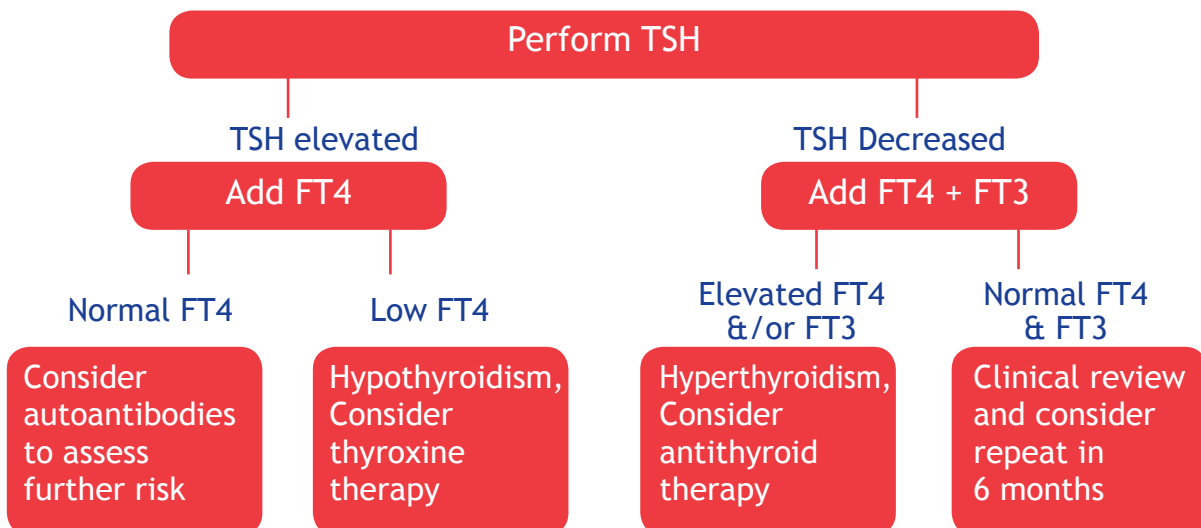
Pregnant patients on replacement - See later section.

Reflex testing

Laboratories retain blood samples for varying lengths of time, making it possible to add additional tests without the need for another blood sample.

If further testing is indicated by the result of the TSH test some laboratories will add FT4, FT3 and thyroid antibodies (this is called 'reflex testing'). However, we do not recommend GPs rely on the laboratory to add extra tests.

Order of testing



If you receive an abnormal thyroid result on a patient it is important you reconsider the clinical picture. Particularly if there are small variations from normal the best approach may be to retest the patient in 4-6 months. Some results may show variation as a result of resolving non-thyroid illness, or biological and analytical variation.

Possible explanations for various result combinations

	High T4	Normal T4	Low T4
High TSH	Irregular use of thyroxine Amiodarone Pituitary hyperthyroidism (TSH-producing pituitary tumour - rare) Thyroid hormone resistance (very rare)	Subclinical hypothyroidism T4 under replacement	Primary hypothyroidism
Normal TSH	As above Some drugs (steroids, beta-blockers, NSAIDs) Non-thyroidal illness T4 replacement (sometimes stabilises with normal TSH and ↑FT4)	Normal	Some drugs (anticonvulsants, anti-T3, anti-T4) Pituitary or hypothalamic hypothyroidism, Severe non-thyroidal illness
Low TSH	Primary hyperthyroidism	Subclinical hyperthyroidism Subtle T4 over replacement Non-thyroidal illness	Pituitary or hypothalamic hypothyroidism, Severe non-thyroidal illness

Adapted from: Topliss DJ, MJA 2004;180:186-93.

Limitations of thyroid function tests

Thyroid function tests are measured by immunoassays that use specific antibodies and are subject to occasional interference. This interference may come from antibodies circulating in the patient's serum which can bind components of the assay and cause unpredictable effects - results obtained may be inappropriately high, low or even not detectable. This may happen to any of the parameters measured. Although this occurs rarely, it must be stressed that results should be interpreted in the context of the clinical picture.

If the laboratory results appear inconsistent with the clinical picture, it may be helpful to communicate this to the laboratory and request the following checks:

- Confirm the specimen identity.
- Reanalyse the specimen using an alternative manufacturer's assay.
- Analyse the specimen for the presence of a heterophilic antibody.

When you are unsure of the relevance of a particular result, a phone call to the pathologist can be extremely helpful.

Monitoring patients on thyroxine

TSH is the most appropriate test when monitoring patients receiving thyroxine for the treatment of hypothyroidism. It should be measured no sooner than 6-8 weeks after the start of treatment. In the unusual situation where thyroid function needs to be assessed before this time, FT4 should be used, as the TSH will not have plateaued at this stage.

Once the target TSH has been reached, a further TSH test in 3-4 months is often helpful to ensure the TSH is stable. Patients on long-term stable replacement therapy usually require only an annual TSH, unless pregnant. The usual goal of treatment for primary hypothyroidism is for the TSH to be within the reference range. Occasionally drugs such as iron, antacids, or HRT may increase the required dose of thyroxine. Therefore drug doses should be separated and if there is doubt, TSH should be rechecked after several weeks.

Biological and assay variability means that minor variations in TSH (e.g. 1-2 mIU/L) are not usually clinically significant.

Monitoring untreated subclinical thyroid disease

Subclinical hypothyroidism - Is defined as an asymptomatic patient with raised TSH levels but normal FT4 concentration. A common cause is Hashimoto's thyroiditis and, many of these patients subsequently develop overt hypothyroidism, especially if thyroid antibodies are positive. The decision to initiate thyroid replacement therapy should be made based on the presence of symptoms; patients with TSH between 5-6 mIU/L usually have no symptoms, while as the TSH approaches 10 mIU/L more symptoms are probable. In the remainder of patients thyroxine should be considered for those with a TSH persistently >10mIU/L. Patients not treated with thyroxine should be monitored using TSH every 6-12 months.

Subclinical hyperthyroidism - Is defined as an asymptomatic patient with a suppressed TSH level and normal FT4 and FT3. Common causes include excessive thyroxine replacement, autonomously functioning multinodular goitre and subclinical Graves disease. These patients are at increased risk of developing atrial fibrillation and possibly osteoporosis. Further investigation and treatment should be considered for patients with an undetectable TSH on repeated testing.

Monitoring patients on anti-thyroid drugs

Following initiation of anti-thyroid medication, the TSH may remain suppressed for 3-6 months. Therefore, it is recommended that thyroid function be monitored every 4 weeks using FT4 and TSH to adjust the dose until the TSH normalises and clinical symptoms have improved. Then the patient can be monitored every 2 months using TSH only.

All patients on anti-thyroid medication should be warned about the rare but serious complication of agranulocytosis. Patients should be instructed to stop treatment if fever, sore throat or other infection develops. Because the onset of agranulocytosis is abrupt, and the occurrence is rare, routine full blood counts are not recommended,¹ instead, patients should be advised to report fever, sore throat or infection.

Thyroid tests in the pregnant patient

Thyroid screening in women planning pregnancy, and those who are pregnant, has been advocated by some groups. This is because subclinical hypothyroidism may be associated with ovulatory dysfunction and infertility; while undetected subclinical hypothyroidism during pregnancy may be associated with hypertension and toxæmia,⁹ and subsequently a slight reduction in the IQ of the offspring. At this stage screening these groups remains controversial and is not recommended, unless there are symptoms of thyroid disease.

TSH may be temporarily suppressed during the first trimester of pregnancy, due to the thyroid stimulating effect of hCG. FT4 levels tend to fall slowly in the second half of pregnancy.

In women with previous mildly abnormal TSH who are considering pregnancy, the TSH should be checked. If the TSH is abnormal, thyroid function should be restored to within the reference limit prior to conception.

In hypothyroid pregnant patients receiving treatment, the goal should be normalisation of both TSH and FT4. The majority of women receiving thyroxine need a dose increase during pregnancy, usually during the first trimester, and a 'proactive' dose increase of 30% has been recommended once pregnancy is confirmed.¹⁰ Dose requirements stabilise by 20 weeks and then fall back to non-pregnant levels after delivery. FT4 should be maintained above the 10th percentile of the range (about 11-13 pmol/L) from week 6 to week 20. There is strong observational evidence that this approach allows optimal foetal neurological development. Thyroid function (especially FT4) should be checked early in pregnancy and at the start of trimesters two and three. More frequent retesting is sometimes indicated (e.g. if thyroxine dose is altered).

Sick euthyroid syndrome

Acute or chronic non-thyroidal illness (sick euthyroid syndrome) has complex effects on thyroid function tests, and in many cases can make some thyroid function tests inherently non-interpretable. During illness, TSH frequently falls, and then may rise temporarily on recovery. There may also be transient changes in the FT4 and FT3. Therefore, it is recommended patients with non-thyroidal illness should have thyroid function testing deferred until the illness has resolved, unless there is history or symptoms suggestive of thyroid dysfunction.¹¹

Thyroid cancer

In patients with thyroid cancer, dosages of thyroxine that produce TSH suppression are intentionally used, because TSH is thought to promote tumour recurrence. TSH should be suppressed, but not to undetectable levels. Anti-thyroglobulin antibodies should also be measured to exclude interference with thyroglobulin assays. Thyroglobulin values below 2 µg/L, in the absence of thyroglobulin antibodies (particularly if TSH is elevated) are a useful negative predictor of residual or recurrent differentiated thyroid cancer.

The effects of drugs on thyroid function

The two drugs that most frequently effect thyroid function are amiodarone and lithium.

Amiodarone - Thyroid function should be checked prior to commencing amiodarone. Mildly abnormal thyroid function tests often occur in the first six months of treatment (mild TSH and FT4 elevation). Patients on long term therapy should be monitored with 6 monthly TSH and FT4 tests. An early repeat should be arranged if there are abnormalities of concern (such as falling TSH) or the patient develops symptoms of thyroid dysfunction.

Amiodarone therapy can induce the development of hypothyroidism or hyperthyroidism in 14-18% of patients.¹¹ Pre-existing Hashimoto's thyroiditis and/or thyroid peroxidase antibodies are a risk factors for developing hypothyroidism during treatment.

Amiodarone-induced hyperthyroidism may also occur during therapy, most commonly in patients with multinodular goitre. Such patients can be difficult to treat and specialist consultation should be considered early; restoration of euthyroidism may take several months after cessation of amiodarone therapy.

Lithium - Lithium can lead to hypothyroidism, especially in patients with underlying autoimmune thyroid disease. An annual check of thyroid function is recommended.

GP and laboratory communication

To provide a better outcome for the patient it is important there is open and clear communication between the GP and the laboratory. It is important the laboratory is aware of the following:

- The clinical indication for testing (are you suspicious of thyroid dysfunction, or are you monitoring drug treatment)
- Any relevant drug treatments the patient may be taking (e.g. thyroxine, carbimazole), including the dose and any changes in dose and the length of therapy.

Providing the laboratory with as much clinical information as possible allows the laboratory to provide a better service. Reflex tests can be added more appropriately, and abnormal or unexpected results can be investigated and interpreted more effectively.

TSH (thyroid stimulating hormone, thyrotropin) - In most situations TSH analysed using a high sensitivity assay is now accepted as the first line test for assessment of thyroid function. A TSH between 0.4 and 4.0 mIU/L gives 99% exclusion of hypo- or hyperthyroidism,¹² while the TSH is considered more sensitive than FT4 to alterations of thyroid status in patients with primary thyroid disease.

FT4 (free thyroxine) - This test measures the metabolically active, unbound portion of T4. Measurement of FT4 eliminates the majority of protein binding errors associated with measurement of the outdated total T4, in particular the effects of oestrogen.

FT3 (free triiodothyronine) - FT3 has little specificity or sensitivity for diagnosing hypothyroidism and adds little diagnostic information. The main value of FT3 is in the evaluation of the 2 to 5% of patients who are clinically hyperthyroid, but have normal FT4. In this situation, an elevated FT3 would be suggestive of T3 toxicosis, in which the thyroid secretes increased amount of T3 or there is excessive conversion of T4 to T3.

Thyroid autoantibodies - The key reason for the measurement of these antibodies is almost entirely for the management of those with abnormal thyroid function. Autoimmune thyroid disease is detected most easily by measuring circulating antibodies against thyroid peroxidase and thyroglobulin (Thyroid peroxidase antibodies are also known as anti-TPO or antimicrosomal antibodies). In subclinical disease, the presence of thyroid antibodies increases the long-term risk of progression to clinically significant thyroid disease about two-fold. Almost all patients with autoimmune hypothyroidism and up to 80% of those with Graves disease have TPO antibodies, usually at high levels, although about 5 to 15% of euthyroid women and up to 2% of euthyroid men will also have thyroid antibodies.

Thyroglobulin - Levels are increased in all types of thyrotoxicosis, except *thyrotoxicosis factita* caused by self-administration of thyroid hormone. The main role for thyroglobulin is in the follow-up of thyroid cancer patients. After total thyroidectomy and radioablation, thyroglobulin levels should be undetectable; measurable levels (>1 to 2ug/L) suggest incomplete ablation or recurrent cancer.

Thyroid stimulating antibody - (Previously called long-acting thyroid stimulating antibodies or LATS) has a role in the diagnosis of Graves disease where other test results are ambiguous. It may also be useful in pregnant women with Graves disease, to determine the likelihood of fetal thyrotoxicosis.

Thyroid function

The function of the thyroid is to secrete hormones which control metabolic pathways and thereby control various physiological functions. The thyroid gland operates in conjunction with the hypothalamus and the pituitary, which is commonly referred to as the "hypothalamic-pituitary-thyroid axis". In addition to the stimulatory cascade leading to thyroid hormone secretion, the axis is also subject to feedback inhibition by the circulating thyroid hormones.

The thyroid gland

The thyroid is a small (25 grams) butterfly-shaped gland located at the base of the throat. It is the largest of the endocrine glands, and consists of two lobes joined by the isthmus. The thyroid hugs the trachea on either side of the second and third tracheal ring, opposite the 5th, 6th and 7th cervical vertebrae. It is composed of many functional units called follicles, which are separated by connective tissue.

Thyroid follicles are spherical and vary in size. Each follicle is lined with epithelial cells which encircle the inner colloid space (colloid lumen). Cell surfaces facing the lumen are made up of microvilli and surfaces distal to the lumen lie in close proximity to capillaries.

The thyroid is stimulated by the pituitary hormone TSH to produce two hormones, thyroxine (T4) and triiodothyronine (T3) in the presence of iodide. Hormone production proceeds by six steps:

1. Dietary iodine is transported from the capillary through the epithelial cell into the lumen.
2. Iodine is oxidized to iodide by the thyroid peroxidase enzyme (TPO) and is bound to tyrosine residues on the thyroglobulin molecule to yield monoiodotyrosine (MIT) and diiodotyrosine (DIT).
3. TPO further catalyzes the coupling of MIT and DIT to form T4 and T3.
4. The thyroglobulin molecules carrying the hormones are taken into the epithelial cells via endocytosis in the form of colloid drops.
5. Proteolysis of the iodinated hormones from thyroglobulin takes place via protease/peptidase action in lysosomes and the hormones are released to the capillaries.
6. Any remaining uncoupled MIT or DIT is deiodinated to regenerate iodide and tyrosine residues.

The pituitary

The pituitary is located at the base of the brain and consists of two lobes, denoted the anterior and posterior lobes. This endocrine gland produces several metabolic hormones that direct crucial functions throughout the body, including regulation of growth, reproduction and metabolism. The pituitary is closely associated with the hypothalamus, which regulates the secretion of pituitary hormones through the release of various neurohormones.

The anterior pituitary is crucial for proper thyroid function through the production and secretion of thyroid stimulating hormone (TSH). TSH secretion is positively regulated by a neurohormone known as thyrotropin releasing hormone (TRH) from the hypothalamus.

The hypothalamus

The hypothalamus is located at the base of the brain and along with the thalamus forms the diencephalon. The hypothalamus directs many processes including peripheral autonomic mechanisms, endocrine activities and many somatic functions, such as regulation of water balance, body temperature, sleep, sexual development and food intake. The hypothalamus secretes several neural hormones which regulate secretion of various pituitary hormones. The neuropeptide TRH is secreted by the hypothalamus and acts to stimulate TSH production in the anterior pituitary.

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