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# Hypothyroidism

## Investigation and management

### Background

Hypothyroidism is a common endocrine disorder that mainly affects women and the elderly.

### Objective

This article outlines the aetiology, clinical features, investigation and management of hypothyroidism.

### Discussion

In the Western world, hypothyroidism is most commonly caused by autoimmune chronic lymphocytic thyroiditis. The initial screening for suspected hypothyroidism is thyroid stimulating hormone (TSH). A thyroid peroxidase antibody assay is the only test required to confirm the diagnosis of autoimmune thyroiditis. Thyroid ultrasonography is only indicated if there is a concern regarding structural thyroid abnormalities. Thyroid radionucleotide scanning has no role in the work-up for hypothyroidism. Treatment is with thyroxine replacement (1.6 µg/kg lean body weight daily). Poor response to treatment may indicate poor compliance, drug interactions or impaired absorption. The significance of elevated TSH associated with thyroid hormones within normal range is controversial; thyroxine replacement may be beneficial in some cases. Unless contraindicated, iodine supplementation should be prescribed routinely in women planning a pregnancy. Where raised TSH levels are detected periconceptually or during pregnancy, specialist involvement should be sought.

### Keywords

hypothyroidism; thyroid diseases



Hypothyroidism is one of the most common endocrine disorders, with a greater burden of disease in women and the elderly.<sup>1</sup> A 20 year follow up survey in the United Kingdom found the annual incidence of primary hypothyroidism to be 3.5 per 1000 in women and 0.6 per 1000 in men.<sup>2</sup> A cross sectional Australian survey found the prevalence of overt hypothyroidism to be 5.4 per 1000.<sup>3</sup>

### Aetiology

Iodine deficiency remains the most common cause of hypothyroidism worldwide.<sup>4</sup> However, in Australia and other iodine replete countries, autoimmune chronic lymphocytic thyroiditis is the most common aetiology.<sup>5</sup>

The main causes of hypothyroidism and associated clinical features are shown in *Table 1*.

### When to suspect hypothyroidism

Symptoms are influenced by the severity of the hypothyroidism, as well as its rapidity of onset. Slow failure of thyroid function caused by autoimmune thyroiditis typically presents insidiously over years.<sup>6</sup> Where the diagnosis is suspected, a neck examination should be performed looking for the presence or absence of a goitre or thyroid nodules, as well as a systematic examination considering both aetiology (eg. thyroidectomy scar, skin changes suggestive of previous external neck irradiation, specific autoimmune diseases such as vitiligo), and signs of hypothyroidism (*Table 2*). The spectrum of clinical presentations range from clinically unapparent disease to myxoedema coma, a rare endocrine emergency.<sup>7</sup> Given the poor specificity of the symptoms of hypothyroidism, patients may manifest clinical features that are suggestive of the diagnosis without any abnormality of thyroid function. Thyroid hormone supplementation in such a situation has shown no clear response and is not justified.<sup>8</sup>

### Investigations

Initial screening is by measuring the thyroid stimulating hormone (TSH) level. If this is elevated, the TSH should be repeated within 2–8 weeks with a free T4 level to confirm the diagnosis. A free T4 level should be ordered if there is a convincing clinical picture for hypothyroidism, despite the absence of TSH elevation, to exclude the (much less common) possibility of central hypothyroidism due to pituitary or hypothalamic pathology (*Figure 1*). Thyroid autoantibodies

**Table 1. Causes of hypothyroidism and associated clinical features**

Cause	Clinical features to elicit
<b>Autoimmune lymphocytic thyroiditis</b> <ul style="list-style-type: none"> <li>• Hashimoto thyroiditis</li> <li>• Atrophic thyroiditis</li> </ul>	Personal or family history of autoimmune conditions. Evidence of specific autoimmune diseases such as vitiligo on examination
<b>Postablative therapy or surgery</b> <ul style="list-style-type: none"> <li>• Radioiodine therapy</li> <li>• Thyroidectomy</li> </ul>	History of previous radioiodine therapy or thyroid surgery Evidence of a surgical scar or skin changes suggestive of previous external neck irradiation on examination
<b>Transient</b> <ul style="list-style-type: none"> <li>• Subacute thyroiditis</li> <li>• Silent thyroiditis</li> <li>• Postpartum thyroiditis</li> <li>• Early postablative therapy</li> </ul>	Preceding history of viral infection, pregnancy or radioiodine ablation Evidence of an enlarged tender thyroid on examination (subacute thyroiditis)
<b>Iodine associated</b> <ul style="list-style-type: none"> <li>• Iodine deficiency</li> <li>• Iodine induced</li> </ul>	Dietary intake history
<b>Drug induced</b> <ul style="list-style-type: none"> <li>• Carbimazole</li> <li>• Propylthiouracil</li> <li>• Iodine</li> <li>• Amiodarone</li> <li>• Lithium</li> <li>• Interferons</li> <li>• Thalidomide</li> <li>• Sunitinib</li> <li>• Rifampicin</li> </ul>	Medication history
<b>Infiltrative</b> <ul style="list-style-type: none"> <li>• Riedel thyroiditis (fibrous thyroiditis)</li> <li>• Scleroderma</li> <li>• Amyloid disease</li> <li>• Haemochromatosis</li> <li>• Infection (eg. tuberculosis)</li> </ul>	Personal history or other systemic features of an infiltrative disorder
<b>Neonatal/congenital</b> <ul style="list-style-type: none"> <li>• Thyroid agenesis/ectopia</li> <li>• Genetic disorders affecting thyroid hormone synthesis</li> <li>• Transplacental passage of TSH receptor blocking antibody</li> </ul>	Family history of thyroid disease/hypothyroidism Maternal medication use during pregnancy
<b>Rare</b> <ul style="list-style-type: none"> <li>• Secondary (pituitary or hypothalamic disease)</li> <li>• Thyroid hormone resistance syndrome</li> <li>• Anomalous laboratory TSH results (eg. caused by heterophil antibodies)</li> </ul>	Other clinical features of pituitary deficiency

(antithyroid peroxidase and antithyroglobulin antibodies) are positive in 95% of patients with autoimmune thyroiditis. The thyroid peroxidase (TPO) antibody assay is sufficiently sensitive and specific to make this the only test now needed to confirm a diagnosis of autoimmune thyroiditis.<sup>5</sup> Antithyroglobulin antibodies are nonspecific and the use of this test is now confined to thyroid cancer follow up. Thyroid peroxidase antibody positivity is seen in 10–15% of the general population<sup>2,3,9</sup> and is not an indication for treatment where there is no biochemical abnormality of thyroid function. Annual thyroid function

testing is recommended in euthyroid patients who have positive antithyroid antibodies, as progression to hypothyroidism is more common in this patient group.<sup>2</sup>

A diagnosis of hypothyroidism in itself is not an indication for thyroid imaging. Thyroid ultrasonography is only indicated to evaluate suspicious structural thyroid abnormalities (ie. palpable thyroid nodules). While thyroid radionucleotide scanning may be useful in elucidating the aetiology of hyperthyroidism, it has no role in the work-up for hypothyroidism. There is an association between chronic thyroiditis and



thyroid nodules, but whether this association is related to an increased risk of thyroid cancer is controversial.<sup>7</sup>

A low serum T4 without the expected increase in serum TSH raises the possibility of central hypothyroidism due to pituitary or hypothalamic pathology (Figure 1). However, as this pattern is also seen transiently during recovery from severe illness, it should be confirmed on a repeat test when the patient is well. Clinical clues for central hypothyroidism include other features of pituitary failure (eg. amenorrhoea, hypotension, fine wrinkling of the skin, abnormal

pallor, hyponatraemia or hypoglycaemia) or features suggestive of a pituitary mass lesion (eg. visual impairment or headache).<sup>9</sup> If central hypothyroidism is suspected, the function of the hypothalamic-pituitary-adrenal axis should be tested and a magnetic resonance imaging (MRI) scan of the pituitary gland obtained.<sup>10</sup> Importantly, if there is associated secondary adrenal failure, thyroid hormone supplementation should only be commenced after glucocorticoid replacement, otherwise an adrenal crisis may be precipitated.<sup>11</sup>

## Management

Thyroxine replacement therapy is the mainstay of treatment for hypothyroidism and is usually lifelong. However, it is important to recognise when the cause of the hypothyroidism is transient or drug induced because this may require no treatment or only short term thyroxine supplementation (Table 1).

## Dosing

The average daily dose of thyroxine is 1.6 µg per kilogram body weight. However, lower initial doses should be considered in patients who are elderly, frail or who have symptomatic angina, as thyroid hormone increases myocardial oxygen demand with the risk of inducing angina or a myocardial infarction. An initial dose of 50 µg/day is appropriate for healthy elderly patients and 25 µg/day or 12.5 µg/day for the very frail and those with symptomatic angina.<sup>10</sup>

Typically, thyroxine is administered on a daily basis. However, due to its half life of approximately 1 week, weekly administration is occasionally an option where compliance is an issue. Its long half life also means dosing should be adjusted at an interval of no less than 6–8 weeks to allow a steady state to be achieved.<sup>12</sup> An appropriate initial target is the relief of symptoms (if present) and a serum TSH within the laboratory range. In patients with persistent symptoms of ill health, then further titration of thyroxine dosage aiming for a TSH level in the lower reference range (eg. 0.4–2.5 mIU/L) is reasonable. A TSH level in the upper half of the reference range is usually acceptable in older persons. Lower TSH targets may be adopted in pregnancy, and in

<b>Table 2. Symptoms, signs and additional investigation findings in hypothyroidism</b>	
<b>Organ system</b>	<b>Symptoms and signs</b>
Appearance	<ul style="list-style-type: none"> <li>• Puffy and pale facies</li> <li>• Dry, brittle hair</li> <li>• Sparse eyebrows</li> <li>• Dry, cool skin</li> <li>• Thickened and brittle nails</li> <li>• Myxoedema – fluid infiltration of tissues</li> </ul>
Energy and nutrient metabolism	<ul style="list-style-type: none"> <li>• Cold intolerance</li> <li>• Weight gain</li> <li>• Fatigue</li> </ul>
Nervous system	<ul style="list-style-type: none"> <li>• Headache</li> <li>• Paraesthesias (including carpal tunnel syndrome)</li> <li>• Cerebellar ataxia</li> <li>• Delayed relaxation of deep tendon reflexes</li> </ul>
Cognitive/psychiatric	<ul style="list-style-type: none"> <li>• Reduced attention span</li> <li>• Memory deficits</li> <li>• Depression</li> </ul>
Cardiovascular	<ul style="list-style-type: none"> <li>• Bradycardia</li> <li>• Diastolic hypertension</li> <li>• Pericardial effusion</li> <li>• Decreased exercise tolerance</li> </ul>
Musculoskeletal	<ul style="list-style-type: none"> <li>• Myalgias</li> <li>• Arthralgias</li> </ul>
Gastrointestinal	<ul style="list-style-type: none"> <li>• Anorexia</li> <li>• Constipation</li> </ul>
Reproductive system	<ul style="list-style-type: none"> <li>• Irregular or heavy menses</li> <li>• Infertility</li> </ul>
<b>Additional investigations</b>	
<ul style="list-style-type: none"> <li>• Hypercholesterolaemia*</li> <li>• Mild anaemia</li> <li>• Hyponatraemia</li> <li>• Raised creatinine kinase<sup>†</sup></li> </ul>	
<p>* Patients with unexplained hypercholesterolaemia may have undiagnosed hypothyroidism</p> <p>† Statin therapy in hypothyroid patients increases the risk of rhabdomyolysis and should be avoided</p> <p>Adapted from www.thyroidmanager.org</p>	

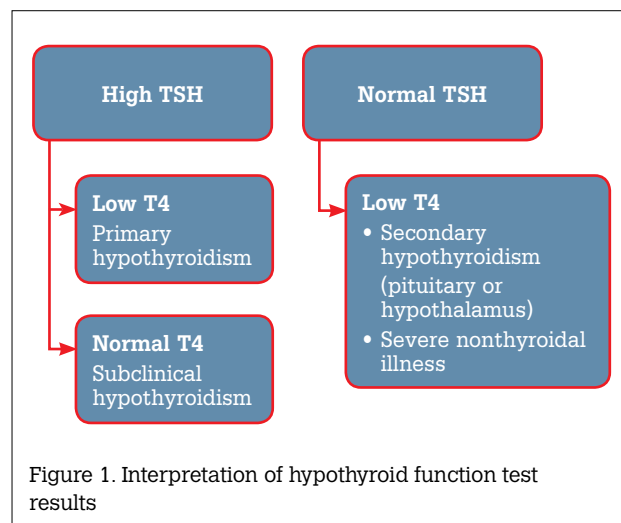


Figure 1. Interpretation of hypothyroid function test results



patients with thyroid cancer, and specialist advice should be sought in these cases (Table 3). In secondary hypothyroidism, TSH is unreliable, and thyroxine dose is adjusted according to free T4 levels, which should be in the mid to normal range.<sup>5</sup>

The thyroxine dose should be increased by 12.5–25 µg/day if the TSH remains above target. In Australia, levothyroxine (LT4) tablets are available in 50, 75, 100 and 200 µg preparations. A practical approach to adjusting thyroxine dosages without cutting tablets would be to use alternate day dosing or to vary the dose depending on the day of the week<sup>8</sup> (eg. Monday to Friday 100 µg with 200 µg on weekends). Once the TSH has normalised, the frequency of review can be reduced to 6 months and then annually thereafter, unless there are situations that may alter thyroxine requirements (eg. significant weight change, commencement of a proton pump inhibitor or the oral contraceptive pill, or plans for pregnancy).

### Side effects

Treatment side effects are rare when the correct dose is given. Fatigue, increased appetite, diarrhoea, nervousness, palpitations, insomnia and tremors are indicative of overtreatment.<sup>13</sup> These symptoms should prompt a repeat TSH level and if suppressed, a reduction in dose of thyroxine. A true allergic reaction to the active ingredient of standard levothyroxine tablets is rare and specialist advice should be sought where alternative therapy (ie. triiodothyronine) is being considered.

### Addressing poor response to treatment

There are a few factors to be considered where biochemical or symptomatic correction is not achieved despite adequate thyroxine dosing. These include compliance, drug interactions and absorption.

### Compliance

Poor compliance is one of the most common reasons for failure to achieve euthyroidism, despite the prescription of otherwise adequate doses of thyroxine.<sup>14</sup> Occasionally, where a patient has been noncompliant for a period of time and takes a large dose of thyroxine before their blood test it results in a pattern of TSH elevation with high to normal or elevated free T4.<sup>10</sup> In these cases it is important to review the frequency of missed tablets with the patient and discuss the importance of treatment compliance.<sup>14</sup>

### Drug interactions

There are a number of drugs that increase thyroxine requirements either by reducing absorption or increasing metabolism. Drugs that have been shown to reduce absorption include:<sup>15</sup>

- calcium carbonate
- ferrous sulphate
- multivitamins
- cholestyramine
- phosphate binders
- proton pump inhibitors.

### Table 3. AACE\* guidelines for indications for referral to a specialist in cases of hypothyroidism<sup>7</sup>

- Patients aged 18 years or less
- Patients unresponsive to therapy
- Pregnant patients
- Cardiac patients
- Presence of goitre, nodule, or other structural changes in the thyroid gland
- Presence of other endocrine disease

\* American Association of Clinical Endocrinologists

Patients should be instructed to take their thyroxine on an empty stomach, at least half an hour before other drugs (this includes espresso coffee).<sup>16</sup> Medicines that may increase thyroxine requirements include:<sup>15</sup>

- the oral contraceptive pill
- anti-epileptic medication (eg. carbamazepine, phenytoin)
- some antibiotics (eg. rifampicin)
- the new tyrosine kinase inhibitors (eg. imatinib).

### Absorption

Much of the variability in replacement thyroxine doses between individuals, after adjustment for body weight, is derived from differences in efficiency of gastrointestinal absorption. Malabsorptive conditions may affect the percentage of the ingested thyroxine dose absorbed and thus increase the required dose. These conditions include small bowel bypass, inflammatory bowel disease, coeliac disease and lactose intolerance. In addition, *Helicobacter pylori* infection and associated chronic gastritis has been found to impair thyroxine absorption. This may improve with treatment of the *H. pylori* infection with combination therapy.<sup>15</sup>

### Persistent symptoms

Symptoms compatible with hypothyroidism may occasionally persist with a TSH level within normal range. In some cases, further dose adjustment to achieve a TSH level in the lower reference range (around 1 mIU/L) may provide symptom resolution.<sup>17,18</sup> However, in a controlled Western Australian trial of escalating doses of thyroxine therapy, there were no differences in measures of wellbeing or quality of life between patients who achieved a TSH target of 0.3, 1.0 or 2.8 mIU/L, respectively.<sup>19</sup> In addition, TSH levels of <0.4 mIU/L have been associated with osteoporosis and atrial fibrillation in people over 60 years of age.<sup>20</sup> Persistent symptoms with low normal TSH levels should prompt a search for other causes such as sleep apnoea, pernicious anaemia or depression. If there is a clear worsening with commencing or increasing thyroxine, co-existing Addison disease should be considered.<sup>11</sup>

Levothyroxine is the preferred way to replace thyroid hormone, and a meta-analysis of 11 randomised studies with more than 1000 patients has shown no obvious benefit of combined levothyroxine and triiodothyronine (T3) therapy.<sup>21</sup> Desiccated thyroid or thyroid hormone extracts, marketed as 'bioidentical hormones' are not a pure product, not approved by the Therapeutic Goods Administration, and have



limited quality control. A recent Endocrine Society of Australia position statement has therefore concluded that, 'in general, desiccated thyroid hormone or thyroid extract, combinations of thyroid hormones or triiodothyronine should not be used as thyroid replacement therapy'.<sup>22</sup>

### Pregnancy and hypothyroidism

Unless contraindicated, iodine supplementation should be prescribed routinely in women planning a pregnancy. The National Health and Medical Research Council recommends an iodine supplement of 150 µg each day.<sup>23</sup> Maternal thyroid function during pregnancy changes in response to the increased metabolic requirements and the presence of the fetus. In addition, thyrotropic activity of β-hCG results in a decrease in TSH in the first trimester.<sup>24</sup> To reflect this adaptation, trimester specific reference intervals for thyroid function tests are recommended.<sup>25</sup> If laboratory reference ranges are not available, the following ranges have been provided by the American Thyroid Association:<sup>24</sup>

- first trimester 0.1–2.5 mIU/L
- second trimester 0.2–3.0 mIU/L
- third trimester 0.3–3.0 mIU/L.

In general, involvement of a specialist is required for the management of raised TSH levels with 4 weekly thyroid function monitoring to 20 weeks gestation, with less frequent monitoring thereafter.<sup>24</sup> The key features of managing hypothyroidism/raised TSH levels during pregnancy are summarised in *Table 4*. There is no clear evidence to recommend population screening with TSH of pregnant women, or of women desiring pregnancy, in the absence of suggestive symptoms or of risk factors for thyroid disease.<sup>24</sup>

### Subclinical hypothyroidism in nonpregnant adults

Subclinical hypothyroidism is defined as a persistently elevated serum TSH with thyroid hormone levels within the reference range. This pattern of thyroid function tests has raised considerable controversy regarding clinical significance and optimum mode of management.<sup>26</sup>

Subclinical hypothyroidism is detected in 4–8% of the general population and in up to 15–18% of women aged more than 60 years.<sup>27</sup> Approximately 4–18% of patients will progress to overt hypothyroidism each year with an increased risk with the following factors:<sup>10</sup>

**Table 4. Definition and management of a raised TSH/hypothyroidism during pregnancy**

	<b>Definition</b>	<b>Concern</b>	<b>Recommended action<sup>24</sup></b>
Overt hypothyroidism (OH) (Prevalence 0.3–0.5%)	TSH >2.5 with low T4 or TSH >10 irrespective of T4 level	Consistent evidence that OH is associated with adverse pregnancy outcomes <sup>29,30</sup> and impaired fetal neurocognitive development <sup>31</sup>	Treatment of OH with levothyroxine is recommended. The goal is to normalise maternal serum TSH values within the trimester specific pregnancy reference range. Commencement of thyroxine while awaiting specialist review is generally appropriate (eg. 50–100 µg/day)
Subclinical hypothyroidism (SCH) (Prevalence 2–2.5%)	TSH between 2.5–10 with normal T4 levels	Evidence is variable as to the effect of SCH on pregnancy and the fetus At this stage, the associated risk of obstetric complications has been more clearly demonstrated than the risk of neurocognitive deficits in the fetus. In addition, TPO Ab positivity may in itself be associated with fetal miscarriage and levothyroxone intervention in TPO antibody positive women with SCH may be beneficial <sup>32</sup>	Options include treatment with levothyroxine to normalise maternal serum TSH or 4 weekly monitoring of TSH Obtain TPO Ab levels while awaiting specialist review
Known history of hypothyroidism	History of hypothyroidism on thyroxine before pregnancy	Normal self regulatory increase in endogenous T4, especially throughout the first trimester, is not achieved by the dysfunctional thyroid gland <sup>33</sup>	Levothyroxine adjustment should be made as soon as pregnancy is confirmed Aim to normalise TSH levels (ie. TSH <2.5) by increasing levothyroxine by two additional tablets weekly or by 25–30% and monitor thyroid function test 4 weekly This adjustment can also be made preconception in women planning pregnancy



- presence of antithyroid antibodies (twofold increase in risk)
- presence of a goitre
- more pronounced TSH elevation
- history of radioiodine ablation therapy, external radiation therapy and chronic lithium therapy.

### The controversy

The significance and hence the benefits of treating subclinical hypothyroidism remains controversial. Potential risks of not treating subclinical hypothyroidism include progression to overt hypothyroidism, cardiovascular effects, dyslipidaemia and neuropsychiatric effects.<sup>7,8,27</sup> A recent Cochrane review<sup>27</sup> found that thyroxine versus no treatment for subclinical hypothyroidism did not improve overall survival, cardiovascular morbidity, health related quality of life or symptoms ascribed to subclinical hypothyroidism. However, there was some evidence to suggest that thyroxine replacement improved surrogate markers for cardiovascular disease such as lipid profile, vascular compliance and left ventricular function.

### Recommended management

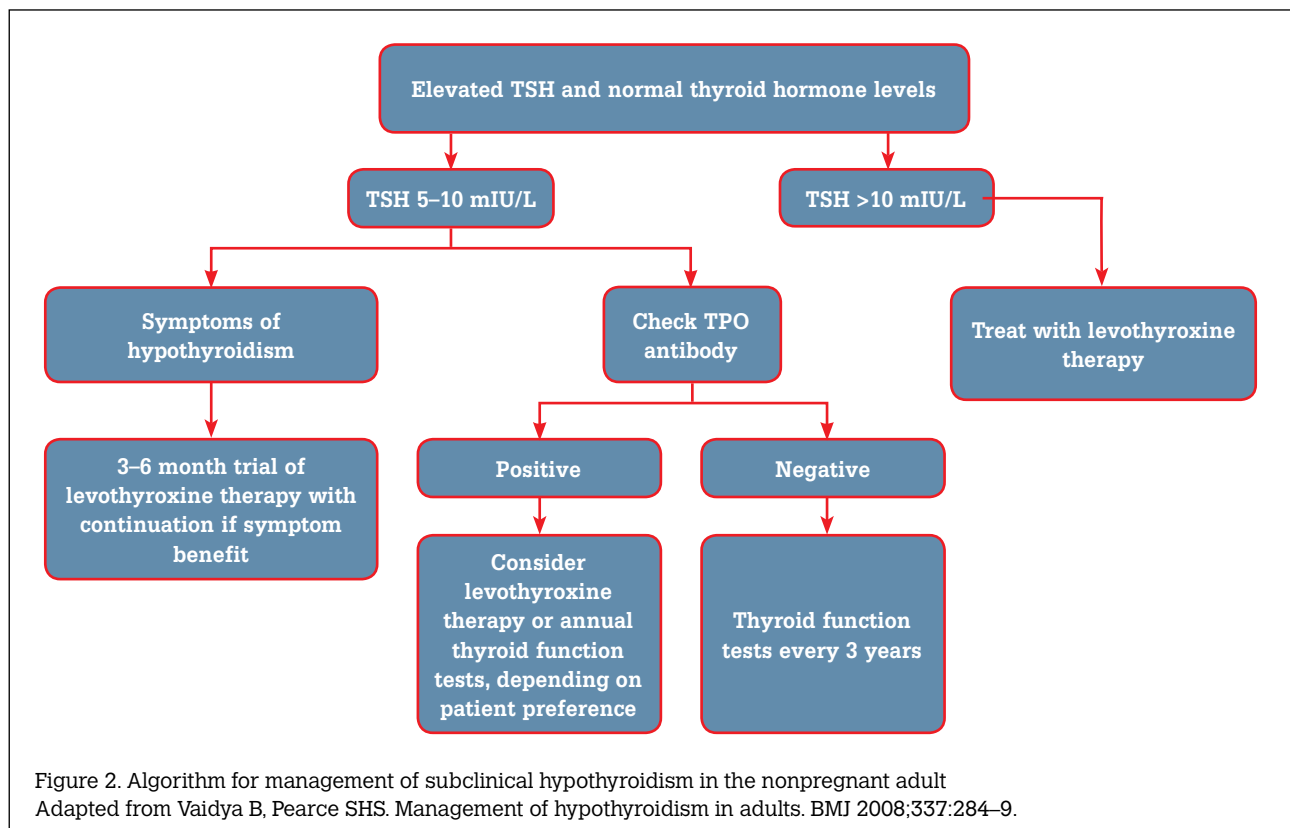
Levothyroxine therapy is usually recommended where the serum TSH is greater than 10 mIU/L.<sup>7</sup> Where the TSH is consistently between 5–10 mIU/L and the patient is symptomatic, a 3–6 month trial of levothyroxine replacement is appropriate. Treatment can be continued where there is symptomatic benefit.<sup>28</sup>

Where the TSH is between 5–10 mIU/L and there is the presence of anti-TPO antibodies, or a goitre, an alternative option to thyroxine therapy would be annual thyroid function tests for early detection of progression to frank hypothyroidism. In contrast, where the patient is antithyroid antibody negative, 3 yearly thyroid function tests are considered sufficient.<sup>28</sup> An algorithm for the management of subclinical hypothyroidism in the nonpregnant adult is shown in *Figure 2*.

Where treatment is commenced, an initial dose of levothyroxine of 25–50 µg/day can be used with a target TSH level between 1.0 and 3.0 mIU/L. The TSH level should be measured in 6–8 weeks after commencement of therapy, and annual reviews once the TSH level is stable.<sup>6</sup>

### Key points

- Iodine deficiency is the most common cause of hypothyroidism worldwide. Autoimmune chronic lymphocytic thyroiditis is the most common aetiology in iodine replete countries such as Australia.
- Initial screening for patients with suspected hypothyroidism is performed by measuring the TSH level.
- A positive thyroid peroxidase antibody assay confirms autoimmune thyroiditis as the cause.
- Thyroid ultrasonography is only indicated to evaluate suspicious structural thyroid abnormalities (ie. palpable thyroid nodules).
- Treatment is with thyroxine replacement (1.6 µg/kg lean body weight daily).





- Poor response to treatment may indicate poor compliance, drug interactions or impaired absorption.
- Thyroxine replacement may be beneficial in some cases of elevated TSH associated with normal thyroid hormone levels, however, this remains controversial.
- Unless contraindicated, iodine supplementation should be prescribed routinely in women planning a pregnancy.

### Resources

- Thyroid Disease Manager is an online, regularly updated resource that includes chapters on all aspects of thyroid disorders from pathophysiology through to management: [www.thyroidmanager.org](http://www.thyroidmanager.org)
- The American Thyroid Association provides clinical and scientific resources for health professionals in addition to patient educational brochures and programs: [www.thyroid.org](http://www.thyroid.org)
- The Endocrine Society of Australia position statement on desiccated thyroid or thyroid extract: [www.endocrinesociety.org.au](http://www.endocrinesociety.org.au).

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Conflict of interest: none declared.

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