Hypothyroidism

For congenital hypothyroidism see the separate Childhood and Congenital Hypothyroidism article.

Hypothyroidism often has an insidious onset but has a significant morbidity. The clinical features are often subtle and nonspecific and may be wrongly attributed to other illnesses, especially in postpartum women and in the elderly.\[1\]

The earliest biochemical abnormality is an increase in serum thyroid-stimulating hormone (TSH) concentration with normal serum fT4 and fT3 concentrations (subclinical hypothyroidism), followed by a decrease in serum fT4, at which stage most patients have symptoms and require treatment (overt hypothyroidism).\[1\]

Epidemiology

- Incidence:
  - Overt form - 2% women, 0.2% men.\[2\]
  - Subclinical - 6-8% women, 3% men.
  - 2.5% of pregnant women develop hypothyroidism.\[3\]
- Hypothyroidism increases with age and is most common around the age of 60 years.
- Autoimmune hypothyroidism is more common in Japan.
- The most common cause of hypothyroidism worldwide is iodine deficiency.
- In areas where iodine deficiency is not a problem, autoimmune and iatrogenic hypothyroidism are more commonly the cause.

Adult hypothyroidism

Hypothyroidism results from insufficient secretion of thyroid hormones and can be due to a variety of abnormalities. The severest form is myxoedema where there is accumulation of mucopolysaccharides in the skin and other tissues, causing thickening of the facial features and associated with ventilatory dysfunction and coma.\[4\]

Aetiology

Primary hypothyroidism
- Autoimmune hypothyroidism - Hashimoto's thyroiditis (associated with a goitre) and atrophic thyroiditis.
- Iatrogenic - radio-iodine treatment, surgery, radiotherapy to the neck - eg, lymphoma (no goitre usually).
- Iodine deficiency - the most common cause worldwide and goitre is present.
- Drugs - amiodarone, contrast media, iodides, lithium and antithyroid medication.
- Congenital defects - eg, absence of thyroid gland or dyshormonogenesis.
- Infiltration of the thyroid - eg, amyloidosis, sarcoidosis and haemochromatosis.

Secondary hypothyroidism
- Isolated TSH deficiency.
- Hypopituitarism - neoplasm, infiltrative, infection and radiotherapy.
- Hypothalamic disorders - neoplasms and trauma.
Transient hypothyroidism
- Withdrawal of thyroid suppressive therapy.
- Postpartum thyroiditis.
- Subacute/chronic thyroiditis with transient hypothyroidism.

Presentation
Often insidious onset with nonspecific symptoms.[5]

Symptoms
- Tiredness, lethargy, intolerance to cold.
- Dry skin and hair loss.
- Slowing of intellectual activity - eg, poor memory and difficulty concentrating.
- Constipation.
- Decreased appetite with weight gain.
- Deep hoarse voice.
- Menorrhagia and later oligomenorrhoea or amenorrhoea.
- Impaired hearing due to fluid in middle ear.
- Reduced libido.

A relationship between hypothyroidism and depression has been assumed for many years. However, the true nature of this association has been difficult to define with many conflicting studies. Large epidemiological studies generally suggest no association between thyroid function and depression in people without thyroid disease. Patients taking thyroxine have poorer psychological well-being than those with no thyroid disease, even if biochemically euthyroid.[6]

Signs
- Dry coarse skin, hair loss and cold peripheries.
- Puffy face, hands and feet (myxoedema).
- Bradycardia.
- Delayed tendon reflex relaxation.
- Carpal tunnel syndrome.
- Serous cavity effusions - eg, pericarditis or pleural effusions.

In autoimmune hypothyroidism, patients may have features of other autoimmune diseases, such as, vitiligo, pernicious anaemia, Addison's disease and diabetes mellitus.[2]

Although most people with hypothyroidism do not have any associated eye problems, hypothyroidism may cause swelling around the eyes, a loss of the hairs in the outer part of the eyebrows, eye discomfort, protruding eyeballs and visual disturbance.[7]

Other presentations
- Acute kidney injury.[8]
Female sexual dysfunction.[9] Hypercholesterolaemia.

This can develop into myxoedema:

- Expressionless dull face with peri-orbital puffiness, swollen tongue, sparse hair.
- Pale, cool skin with rough, doughy texture.
- Enlarged heart.
- Megacolon/intestinal obstruction.
- Cerebellar ataxia.
- Psychosis.
- Encephalopathy.

Patients can go on to develop myxoedema coma (see below).

Hashimoto's and atrophic thyroiditis

- Subclinical autoimmune thyroiditis probably represents the early stages of chronic thyroiditis with a soft or firm thyroid gland which is usually normal in size or slightly enlarged.
- Subclinical autoimmune thyroiditis is associated with normal thyroid function.
- Hashimoto's thyroiditis and atrophic thyroiditis probably represent two ends of the same spectrum of chronic thyroiditis. In Hashimoto's thyroiditis there is a painless goitre of varying size with a rubber consistency and irregular surface. Thyroid function varies from normal to subclinical or overt hypothyroidism.
- Atrophic thyroiditis represents the end stage of autoimmune hypothyroidism and patients are overtly hypothyroid.
- Interestingly, excessive iodine intake can lead to autoimmune hypothyroidism.[10]
- Autoimmune hypothyroidism is uncommon in children. It presents as delayed growth and facial maturation. Puberty may also be delayed. In very young children there may be intellectual impairment.

Postpartum thyroiditis

This occurs in 5-7% of pregnancies within the first six months postpartum.[9] Most women show complete remission but some may progress to permanent hypothyroidism.

Subacute thyroiditis

Also referred to as granulomatous, giant cell or de Quervain's thyroiditis - a viral infection produces local symptoms and exquisite tenderness of the thyroid gland with nodularity. Initially patients are thyrotoxic but later they become hypothyroid.[11]

Investigations[12]

The symptoms of hypothyroidism are not specific to underactivity of the thyroid gland and it is therefore essential to diagnose hypothyroidism with TFTs because it can be dangerous to take levothyroxine or other thyroid hormones if they are not clinically indicated.

The only validated method of testing thyroid function is by blood test, which must include measurement of serum TSH and free thyroxine (fT4).

<table>
<thead>
<tr>
<th>Condition</th>
<th>TSH</th>
<th>Free T4</th>
<th>Free T3</th>
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</thead>
<tbody>
<tr>
<td>Thyroid hormone resistance</td>
<td>Raised or normal</td>
<td>Raised</td>
<td>Raised</td>
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<tr>
<td>Primary hypothyroidism</td>
<td>Raised</td>
<td>Lowered</td>
<td>Lowered or normal</td>
</tr>
<tr>
<td>Secondary hypothyroidism</td>
<td>Lowered or normal</td>
<td>Lowered</td>
<td>Lowered of normal</td>
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- Anti-thyroid peroxidase (anti-TPO) antibodies or anti-thyroglobulin antibodies are found in 90-95% of patients with autoimmune thyroiditis.
- Untreated hypothyroidism may be associated with a raised CK, raised cholesterol and triglycerides and anaemia (normocytic or macrocytic). These abnormalities usually resolve with treatment.
- If the patient has an asymmetrical goitre then they may need imaging of their thyroid gland - eg, ultrasonography - to rule out neoplastic lesions.

Neonates - investigations include ultrasonography or 123I scintigraphy, serum thyroglobulin and low molecular weight iodopeptides to differentiate different types of defects. Total urinary iodine excretion will differentiate between inborn errors of metabolism and hypothyroidism due to iodine deficiency or excess.

Management

Clinical hypothyroidism[12]
When a sufficient dose of thyroid treatment is given to lower the TSH to within the normal reference range for the test method used, patients usually recover from the symptoms of hypothyroidism. Some patients may require fine-tuning of TSH levels inside the reference range.

Patients whose thyroid blood tests are within the reference ranges but who have continuing symptoms, whether on levothyroxine or not, should be further investigated for a non-thyroid cause of their symptoms.

There is very strong evidence for the use of thyroxine (T4 or tetra-iodothyronine) alone in the treatment of hypothyroidism, with this usually being prescribed as levothyroxine. Prescribing of additional tri-iodothyronine (T3) is currently not recommended.

For adults aged over 18 years, the initial dose of levothyroxine is 50-100 micrograms once daily, adjusted in steps of 25-50 micrograms every 3-4 weeks according to response. The usual maintenance dose is 100-200 micrograms once daily.\[13\]

There are certain patients for whom the recommended initial dose of levothyroxine is 25 micrograms once daily, adjusted in steps of 25 micrograms every four weeks according to response. These include: \[13\]

- Patients with cardiac disease.
- Patients with severe hypothyroidism.
- Patients aged over 50 years.

There are potential risks from T3 therapy, including osteoporosis and cardiac arrhythmias. However, over-treatment with T4, when given alone, has similar risks.

Once stabilised, check TSH annually. Free T4 is more useful in secondary hypothyroidism. The patient needs to be informed that symptom relief may take many months and even up to six months after TSH levels have normalised.

Drugs, such as ferrous sulfate, calcium supplements, rifampicin and amiodarone can interfere with T4 absorption.

Subclinical hypothyroidism\[14\]

- Subclinical hypothyroidism occurs when a patient has a TSH level above the upper limit of the reference range (but usually less than 10 mU/L) and free T4 levels are within the reference range.\[12, 15\]
- The population prevalence of subclinical hypothyroidism is approximately 5-10%.
- Subclinical hypothyroidism is common and increases with age. It affects up to 18% of the elderly, with a higher prevalence in women compared to men.\[16\]
- Some patients with subclinical hypothyroidism, especially those whose TSH level is greater than 10 mU/L, may benefit from treatment with levothyroxine in the same way as for clinical hypothyroidism.\[12\]
- Subclinical hypothyroidism is associated with reduced exercise capacity but there is some controversy over whether to treat these patients - symptoms may improve on T4 but there are concerns over risk of reduced bone mineral density and atrial fibrillation.\[2, 17, 18\]
- Treat patients with a history of radio-iodine treatment or positive thyroid antibody test, as this subgroup will nearly always progress to overt hypothyroidism.
- Also treat if there has been previous treatment of Graves’ disease or other organ-specific autoimmune disease or TSH is >10. Levothyroxine is used to maintain TSH within the normal range.\[17\]
- If none of the above is present, then monitor TSH every 6-12 months. If symptomatic then a trial of thyroxine may be warranted.

Treatment of hypothyroidism in special groups

Children

- Very rarely, levothyroxine therapy can cause pseudotumour cerebri in children.
- It is an idiosyncratic reaction and presents with raised intracranial pressure and can occur months after treatment.
Pregnancy

- Women of childbearing age should be encouraged to wait until they are euthyroid before trying to conceive.\[19]\n- It is important to maintain a euthyroid state throughout pregnancy, especially during the first trimester.\[3]\n- Measure TFTs during the first, second and third trimesters for all pregnant women with known hypothyroidism. There is continuing debate as to whether there is a need to screen all pregnant women for thyroid disorders.\[27]\n- TSH is a sensitive marker of thyroid dysfunction during pregnancy.\[20]\n- Treating clinical and subclinical hypothyroidism may reduce adverse obstetric outcomes.\[21]\n- Levothyroxine dose may need to be increased by more than 50% during pregnancy. The dose can usually be reduced postpartum.\[19]\n
Older patients and comorbidity\[13]\n
There are certain patients for whom the recommended initial dose of levothyroxine is 25 micrograms once daily, adjusted in steps of 25 micrograms every four weeks according to response. These include:

- Patients with cardiac disease.
- Patients with severe hypothyroidism.
- Patients aged over 50 years.

Myxoedema coma\[22]\n
- Myxoedema coma is seen mostly in elderly patients and is associated with a mortality rate between 20% and 50%.
- Patients may be on treatment for hypothyroidism or be previously undiagnosed.
- Infections and discontinuation of thyroid supplements are the major precipitating factors.\[23]\n- Patients present with:
  - A reduced level of consciousness.
  - Seizures,\[24]\n  - Hypothermia.
  - Features of hypothyroidism.

- Precipitating factors include sedative drugs and anything that impairs the respiratory system - eg, pneumonia, cardiac failure and myocardial infarction.\[25]\n- Hypoventilation plays a major role with resulting hypoxia and hypercapnia.
- Metabolic disturbances are also prominent, including hyponatraemia and hypoglycaemia.

Treatment

- Intravenous levothyroxine is used - usually start with a loading dose and then a lower dose for maintenance on a daily basis.
- Other treatments that have been used are liothyronine (T3) but this can cause arrhythmias.
- Combinations of levothyroxine and liothyronine can also be used - but the mainstay of therapy is levothyroxine alone.
- Other therapy is usually supportive - eg, correct metabolic disturbances, patient warming if hypothermic and treatment of precipitating factors.
- Patients may need to be intubated and ventilated if respiratory impairment is severe.\[25]\n- Intravenous hydrocortisone is also required, as impaired adrenal function is present in profound hypothyroidism (but send a renal blood cortisol first).

Further reading & references

- Hypothyroidism; NICE CKS, February 2011 (UK access only)
- Management of primary hypothyroidism: statement by the British Thyroid Association Executive Committee; British Thyroid Association (2015)

1. UK Guidelines for the Use of Thyroid Function Tests; British Thyroid Association (2006)
4. Skin problems associated with thyroid disease; DermNet NZ
12. The diagnosis and management of primary hypothyroidism; Royal College of Physicians and others (June 2011)
13. British National Formulary (BNF); NICE Evidence Services (UK access only)
14. 2013 ETA Guideline: Management of Subclinical Hypothyroidism; European Thyroid Association (Nov 2013)
22. Wiersinga WM; Myxedema and Coma (Severe Hypothyroidism)

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