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Hypothyroidism

For congenital hypothyroidism see the separate Childhood and Congenital Hypothyroidism article. There are also separate articles on Subclinical Hypothyroidism, Thyroid Disease in Pregnancy and Myxoedema Coma.

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.

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).

Hypothyroidism epidemiology[1]

The prevalence of hypothyroidism varies according to the definition used, the population characteristics, and the geographical area studied. The prevalence increases in women and with increasing age.

- One European meta-analysis found the total prevalence (diagnosed and undiagnosed) of hypothyroidism to be 3%. The prevalence of undiagnosed hypothyroidism was 4.9% (6.4% in females and 3.4% in males). Of these, the prevalence of overt hypothyroidism was 0.8% in females and 0.3% in males, and the prevalence of subclinical hypothyroidism was 5.9% in females and 3.4% in males.
- A retrospective analysis of General Practice data in the North East of England found the overall prevalence of treated hypothyroidism to be 4.5% in 2016. The prevalence increases with increasing age and is up to 10 times more common in women.

- A review of UK national databases found the prevalence of treated hypothyroidism increased from 2.3% to 3.5% of the total UK population between 2005 and 2014. The prevalence of treated hypothyroidism was positively associated with female sex, white ethnicity, and obesity.
- The British Thyroid Association notes that subclinical hypothyroidism affects 5-10% of the population.
- The true prevalence of subclinical hypothyroidism may have been overestimated in older people, due to the physiological increase in TSH levels with increasing age, that may be misinterpreted as thyroid disease.
- Secondary hypothyroidism is rare. The estimated incidence varies between 1 per 20,000 and 1 per 80,000 people
- The European Thyroid Association guidelines state that the prevalence of overt hypothyroidism in pregnancy is 0.2-0.5%, and subclinical hypothyroidism in pregnancy is 2-2.5%.
- The prevalence of postpartum thyroiditis in iodine-sufficient areas is stated as being about 5-7%.

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.[2]

Hypothyroidism causes (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.

Hypothyroidism symptoms (presentation)

Often insidious onset with nonspecific symptoms.[3]

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.[4]

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.

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.[5]

Other presentations

- Acute kidney injury.[6]
- 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.
- Excessive iodine intake can lead to autoimmune hypothyroidism.
- 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. [7] 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.

Investigations

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

Offer tests for thyroid dysfunction to adults, children and young people with type 1 diabetes or other autoimmune diseases, or new-onset atrial fibrillation. Also consider tests for those with depression or unexplained anxiety. In addition for children and young people with abnormal growth, or unexplained change in behaviour or school performance.

Be aware that symptoms of thyroid dysfunction may be mistaken for menopause.

The National Institute for Health and Care Excellence (NICE) suggests measuring thyroid stimulating hormone (TSH) alone for adults and if the TSH is above the reference range, measure free thyroxine (FT4) in the same sample. If the TSH is below the reference range, measure FT4 and free tri-iodothyronine (FT3) in the same sample.[8]

Condition	TSH	Free T4	Free T3
Thyroid hormone resistance	Raised or normal	Raised	Raised
Primary hypothyroidism	Raised	Lowered	Lowered or normal
Secondary hypothyroidism	Lowered or normal	Lowered	Lowered of normal

- Anti-thyroid peroxidase (anti-TPO) antibodies or anti-thyroglobulin antibodies are found in 90-95% of patients with autoimmune thyroiditis. NICE recommends measuring thyroid peroxidase antibodies (TPOAbs) for adults with TSH levels above the reference range, but not repeating TPOAbs testing.[8]
- 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 ^{123}I 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.

Hypothyroidism treatment and management[8][9]

Referral[1]

- Arrange emergency admission if a serious complication such as myxoedema coma is suspected.
- Arrange urgent referral to an endocrinologist for specialist assessment of the underlying cause if secondary hypothyroidism is suspected.

- Arrange referral or discuss with an endocrinologist the urgency, depending on clinical judgement, if the person:
    - Has suspected subacute thyroiditis.
    - Has a goitre, nodule, or structural change in the thyroid gland. If malignancy is suspected, refer using a suspected cancer pathway.
    - Has suspected associated endocrine disease, such as Addison's disease. Do not start thyroid hormone replacement before specialist glucocorticoid replacement in suspected adrenal failure, as this can precipitate an adrenal crisis.
    - Is female and is planning a pregnancy.
    - Has atypical or difficult to interpret thyroid function tests (TFTs), such as a low thyroid-stimulating hormone (TSH) with low free thyroxine (FT4) level.
    - Has a suspected underlying cause of hypothyroidism, such as drug treatment with amiodarone or lithium.
- Consider referral to an endocrinologist if a person is taking:
    - Adequate or escalating LT4 doses and the TSH level is persistently raised, and underlying causes have been excluded or managed.
    - Adequate or escalating LT4 doses and symptoms of hypothyroidism persist, and alternative causes for symptoms have been excluded.
    - Combination therapy or LT3 monotherapy on specialist advice with uncertain benefits, and a switch to LT4 is being considered.

Overt hypothyroidism

- Offer levothyroxine sodium as first-line treatment and aim to maintain thyroid-stimulating hormone (TSH) levels within the reference range. If symptoms persist, even after achieving normal TSH levels, consider adjusting the dose to achieve optimal well-being whilst avoiding doses that cause TSH suppression or thyrotoxicosis.

- For patients whose TSH level was very high before starting treatment or who have had a prolonged period of untreated disease, the TSH level can take up to six months to return to the reference range.
- Consider measuring TSH levels every three months until a stable level has been achieved, then yearly thereafter. Monitoring free thyroxine (FT4) should also be considered in those who continue to be symptomatic.
- Due to the uncertainty around the long-term adverse effects and the insufficient evidence of benefit over levothyroxine monotherapy, the use of natural thyroid extract is not recommended. Liothyronine (either alone or in combination with levothyroxine) is not routinely recommended but see the section on liothyronine immediately below.

Liothyronine .
NHS England guidance states that liothyronine (L-T3) should not be initiated in primary care for any new patient, and that individuals currently prescribed liothyronine should be reviewed by a consultant NHS endocrinologist with consideration given to switching to levothyroxine (L-T4) where clinically appropriate. Prescriptions for individuals receiving liothyronine should continue until that review has taken place.

The majority of patients can be treated effectively with levothyroxine alone, but liothyronine is perceived to be an important medicine for a small proportion of patients in order to maintain health and well-being.

The prescribing of liothyronine monotherapy or combination therapy with levothyroxine is only supported if initiated by, or considered appropriate following a review by, an NHS consultant endocrinologist. The withdrawal or adjustment of liothyronine treatment should also only be undertaken by, or with the oversight of, an NHS consultant endocrinologist.

Where General Practitioners are involved in such treatment changes this should be with NHS consultant endocrinologist support.

If a patient is initiated on treatment, prescribing responsibility should remain with the hospital consultant for at least three months. TSH levels should be monitored, and free L-T4/free L-T3 levels measured where clinically appropriate.

Subclinical hypothyroidism

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. See also the separate article on Subclinical Hypothyroidism.

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.

See also the separate article on Childhood and Congenital Hypothyroidism.

Pregnancy

Refer all females with hypothyroidism who are planning a pregnancy or are pregnant, to an endocrinologist. For those planning a pregnancy and whose thyroid function tests (TFTs) are not within range, advise delaying conception until stabilised on levothyroxine sodium treatment. If there is any uncertainty about treatment initiation or dosing, discuss this with an endocrinologist whilst awaiting review.

TFTs may produce misleading results in pregnancy and trimester-related reference ranges should be used. If pregnancy is confirmed, urgently measure TFTs. Discuss the initiation, or changes to levothyroxine sodium treatment and TFT monitoring with an endocrinologist whilst awaiting review, to reduce the risk of obstetric and neonatal complications.

See also the article on Thyroid Disease in Pregnancy.

Older patients and comorbidity

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.

Secondary hypothyroidism

If secondary hypothyroidism is suspected, refer the patient urgently to an endocrinologist to assess the underlying cause.

Complications[1]

The potential complications of untreated or undertreated hypothyroidism include:

- Impaired quality of life due to symptoms such as fatigue.
- Dyslipidaemia.
- Metabolic syndrome.
- Coronary heart disease (CHD) and stroke.
- Heart failure.
- Infertility and subfertility.
- Untreated overt hypothyroidism in pregnancy, which is associated with an increased risk of miscarriage, anaemia, pre-eclampsia, placental abruption, postpartum haemorrhage, and stillbirth.
- Adverse neonatal outcomes including preterm delivery, low birth weight, neonatal respiratory distress, congenital abnormalities, congenital hypothyroidism, and impaired fetal neurocognitive development.
- Untreated subclinical hypothyroidism and thyroid autoimmunity in pregnancy: may be associated with an increased risk of miscarriage, pregnancy loss, preterm delivery, low birth weight, gestational diabetes, gestational hypertension, and pre-eclampsia.
- Overt hypothyroidism, which is associated with decreased taste, vision, or hearing, and with impaired attention, concentration, memory, language, executive function, and psychomotor speed.
- Myxoedema coma.

The risks of over-treatment with thyroid hormones include atrial fibrillation, osteoporosis and bone fractures.

Prognosis[1]

- The prognosis of overt primary hypothyroidism is usually good, and most people will recover full physical and psychological well-being following adequate thyroid hormone replacement, which is usually needed for life.
- About 5-10% of people have persistent symptoms (such as impaired well-being and cognitive disturbance) after six months of thyroid hormone treatment, even when thyroid function tests have normalised.
- Spontaneous remission is rare.

Further reading

- Okosieme O, Gilbert J, Abraham P, et al; Management of primary hypothyroidism: statement by the British Thyroid Association Executive Committee. Clin Endocrinol (Oxf). 2016 Jun;84(6):799-808. doi: 10.1111/cen.12824. Epub 2015 Jun 25.
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