Management of hypothyroidism in adults

Bijay Vaidya,[1] Simon H S Pearce[2]

[1]Department of Endocrinology, Royal Devon and Exeter Hospital, Exeter EX2 5DW, and Peninsula Medical School, Exeter

[2]Endocrine Unit, Royal Victoria Infirmary and Newcastle University, Newcastle upon Tyne

Correspondence to: B Vaidya
bijay.vaidya@pms.ac.uk

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Hypothyroidism is one of the commonest chronic disorders in Western populations. In the United Kingdom, the annual incidence of primary hypothyroidism in women is 3.5 per 1000 and in men 0.6 per 1000.[1] During 2006 12 million prescriptions for levothyroxine (50 µg or 100 µg tablets) were dispensed in England, equivalent to about 1.6 million people taking long term thyroid replacement therapy, about 3% of the population.[2] The management of hypothyroidism is generally considered straightforward and is mostly carried out in primary care in the UK. Cross sectional surveys of patients taking levothyroxine have, however, shown that between 40% and 48% are either over-treated or under-treated.[3 4] Furthermore, a small but significant proportion of patients continue to feel unwell despite taking levothyroxine.[5] This review discusses current approaches in the management of hypothyroidism in adults.

What are the causes of hypothyroidism?

Box 1 lists the important causes of hypothyroidism. The commonest cause of hypothyroidism in developed countries is autoimmune thyroiditis, which may be associated with a goitre (Hashimoto's thyroiditis) or, with equal frequency, thyroid atrophy. Radioiodine ablation or surgical thyroidectomy as treatment for hyperthyroidism or thyroid cancer are also responsible for important numbers of patients with hypothyroidism. Less often, hypothyroidism may be drug induced (suggesting the possibility of reversibility) or be secondary to disorders of the pituitary or hypothalamus (central or secondary hypothyroidism). Congenital hypothyroidism, due either to thyroid aplasia or hypoplasia or to defective biosynthesis of thyroid hormones, occurs in one per 4000 live births.[6] In some parts of the world iodine deficiency remains highly prevalent, with consequent developmental deficits and hypothyroidism affecting infants and children.

How do patients with hypothyroidism present?

Autoimmune thyroiditis generally causes a slow failure of thyroid hormone production, thus symptoms may be insidious, developing over years.[1] The spectrum of presentation ranges from fatigue or mild forgetfulness to a severe impairment of consciousness, termed "myxoedema coma" (box 2). Advanced presentations of hypothyroidism are rarely seen nowadays in developed countries.

How to diagnose hypothyroidism?

The diagnosis of primary hypothyroidism is confirmed by an increase in the serum thyroid stimulating hormone concentration above the upper limit of the reference range. Adults presenting with symptomatic hypothyroidism often have a thyroid stimulating hormone level in excess of 10 mU/l, coupled with a reduction in the serum free or total thyroxine concentration below the reference range. Some adults have less severe hypothyroidism, with a serum thyroid stimulating hormone that is increased (typically between 5 mU/l and 10 mU/l) but a serum thyroxine concentration within the reference range. This is termed subclinical hypothyroidism (also called mild hypothyroidism) and in many patients it represents a state of compensated or mild thyroid failure. About a 30% diurnal variation occurs in thyroid stimulating hormone levels, with a trough around 2 00 pm and rising during the hours of darkness. This variability is conserved in mild hypothyroidism, sometimes giving the impression of fluctuating disease.[7] A small variability also exists between the different assays used for measuring thyroid stimulating hormone levels and the reference ranges quoted by different laboratories. Serum triiodothyronine concentration is often normal even in severe hypothyroidism and is not a helpful investigation in this situation. If the cause is autoimmune, circulating antibodies directed at thyroid

Sources and selection criteria

We searched PubMed and the Cochrane Library databases for the keywords hypothyroidism and thyroxine. We identified further references from the original articles and recent review articles. We studied articles only in the English language, and gave priority to those published in the past 10 years and those reporting randomised controlled trials.

Box 1 Important causes of hypothyroidism

Autoimmune thyroiditis—Hashimoto's thyroiditis, atrophic autoimmune thyroiditis

Iatrogenic—thyroidectomy, radioiodine therapy

Thyroiditis—subacute thyroiditis (also known as De Quervain's thyroiditis), silent thyroiditis, postpartum thyroiditis

Iodine deficiency

Drugs—carbimazole, methimazole, propylthiouracil, iodine, amiodarone, lithium, interferons, thalidomide, sunitinib, rifampicin

Congenital hypothyroidism—thyroid aplasia or hypoplasia, defective biosynthesis of thyroid hormones

Disorders of the pituitary or hypothalamus (secondary hypothyroidism)

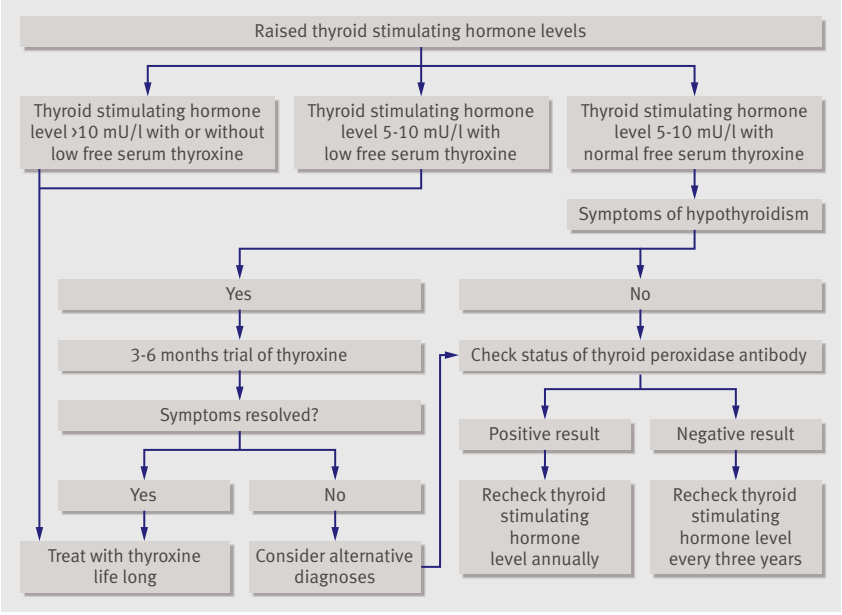
peroxidase (formerly known as microsomal antibodies) or thyroglobulin are detectable in more than 90% and about 70% of patients, respectively.

Whom to treat for hypothyroidism?

The figure shows a pragmatic algorithm for the management of primary hypothyroidism in non-pregnant adults.

Overt hypothyroidism with thyroid stimulating hormone concentrations >10 mU/l

Symptomatic people with thyroid stimulating hormone concentrations above 10 mU/l should be treated.[8 9] As treatment is likely to be life long, it is good practice to confirm the increase in thyroid stimulating hormone on a second sample. Adults with symptomatic overt hypothyroidism usually feel better with treatment. In addition, treatment may reverse the associated dyslipidaemia, with a consequent improvement in vascular risk.[10] Unless the patient has drug induced hypothyroidism (for example, lithium, amiodarone, interferons) or is in the recovery phase of a thyroiditis (for example, postpartum thyroiditis or painful subacute thyroiditis), there is little chance of spontaneous recovery from this degree of hypothyroidism.



Algorithm for pragmatic management of primary hypothyroidism in non-pregnant adults

Subclinical (mild) hypothyroidism: thyroid stimulating hormone between 5 and 10 mU/l (free serum thyroxine in reference range)

Whether people with subclinical hypothyroidism should be treated with thyroxine is controversial. Some of these patients have symptoms of hypothyroidism. A 20 year follow-up study showed a small risk of progression to overt hypothyroidism, which correlates with the level of thyroid stimulating hormone and the presence of thyroid peroxidase antibodies.[1] In addition, two recent meta-analyses have shown an association between subclinical hypothyroidism and cardiovascular morbidity and mortality[11 12]; however, another meta-analysis failed to show a benefit of thyroxine replacement in reducing these adverse outcomes.[13] In people aged more than 85 years, evidence suggests that subclinical hypothyroidism is associated with longevity.[14] A recent scientific review by an expert panel did not support the routine use of thyroxine in subclinical hypothyroidism.[9]

In practice the level of thyroid stimulating hormone should be remeasured, along with doing a test for thyroid peroxidase antibodies, within three months of the initial test to ascertain the persistence of the abnormal level of thyroid stimulating hormone and the tempo of the thyroid failure. A transient, modest increase in hormone levels may be found during recovery from non-thyroidal illness. If patients have symptoms consistent with hypothyroidism and the increase in thyroid stimulating hormone persists, then a therapeutic trial of levothyroxine for three to six months is a reasonable approach. If the patient feels improved by therapy—as a third to one half do—it is reasonable to continue treatment. If patients do not have symptoms and the hormone level seems stable with thyroid peroxidase antibodies present, the risk of progression to overt hypothyroidism is a little less than 5% per year[1] and so a yearly surveillance strategy for thyroid stimulating hormone level is satisfactory. If thyroid peroxidase antibodies are absent, then surveillance of thyroid stimulating hormone levels every three years is the current recommendation,[8] with the risk of progression to overt hypothyroidism being around 2% per year. The exception to the above is in pregnancy, or in someone trying to conceive, when mild hypothyroidism should always be treated.

Patients with symptoms of hypothyroidism but normal thyroid stimulating hormone levels

Although a normal level of thyroid stimulating hormone excludes primary thyroid failure, if the result of a serum free thyroxine assay is not available then secondary hypothyroidism from pituitary or hypothalamic disease could be present. This is almost always associated with other hormonal deficiencies and resulting clinical clues (for example, low gonadotrophin levels

Box 2 Presenting features of hypothyroidism

- Exhaustion
- Somnolence
- Slow cognition
- Intolerance to cold
- Constipation
- Depression
- Weight gain
- Calf stiffness
- Menstrual disturbance
- Carpal tunnel syndrome
- Hearing impairment
- Dry, thin and pale skin
- Puffiness below the eyes
- Bradycardia
- Slow relaxing tendon reflexes
- Coarsening of facial features
- Pleural effusion
- Pericardial effusion
- Ascites
- Non-pitting oedema of lower leg
- Hyponatraemia
- Hypercholesterolaemia
- Impaired consciousness (myxoedema coma)

in a postmenopausal woman, amenorrhoea, galactorrhoea, erectile dysfunction). Owing to the possibility of secondary adrenal failure, a full evaluation of pituitary function is important before starting levothyroxine in secondary hypothyroidism. A small but carefully done clinical trial has shown that people with symptoms of hypothyroidism but a normal serum thyroid stimulating hormone level do not get any improvement in their symptoms with levothyroxine therapy.[15]

How to treat hypothyroidism?

Levothyroxine is the treatment of choice for hypothyroidism.[8] Although levothyroxine is commonly titrated upwards from a starting dose of 25-50 μg daily, a randomised controlled trial has shown that this approach is not necessary for most patients and is likely to be wasteful of resources.[16] So for most patients a full replacement dose of levothyroxine should be started. The exceptions to this are patients aged more than 60 years or those with ischaemic heart disease. The requirement for levothyroxine depends on lean body mass, and a daily dose of 1.6 μg/kg body weight will render most patients euthyroid.[17] This dose equates to 100 μg daily for the average sized woman (60 kg) and 125 μg daily for the average sized man (75 kg). When giving a trial of levothyroxine therapy for subclinical hypothyroidism, it is worth starting with close to a full replacement dose (75 or 100 μg daily), on the basis that it would be difficult to be sure if the symptoms might not be caused by hypothyroidism, until a therapeutic dose of levothyroxine has been tried.

How to monitor levothyroxine replacement

Measurement of serum thyroid stimulating hormone is the cornerstone of monitoring levothyroxine replacement, the exception being people with pituitary disease. In longstanding untreated hypothyroidism there is pituitary thyrotroph hyperplasia, so the level of thyroid stimulating hormone commonly takes three to six months to fall into the reference range, even with full dose initial replacement therapy. After starting levothyroxine, thyroid stimulating hormone and free thyroxine levels should be measured at eight to 12 weeks and adjustments made to the dose accordingly. Although measuring thyroid stimulating hormone levels annually is sufficient for someone receiving a stable dose of levothyroxine, certain situations are predictably associated with a change in levothyroxine requirement, particularly pregnancy, but to a lesser degree oestrogen use and after large changes in body weight.[18,19] The dose of levothyroxine tends to decrease with advancing age owing to decreased clearance of thyroxine and a reduction in lean body mass.[20]

What is the target level for thyroid stimulating hormone?

The aim of levothyroxine treatment is to make the patient feel better, and the dose should be adjusted to maintain the level of thyroid stimulating hormone within the lower half of the reference range,[21] around 0.4 to 2.5 mU/l. If the patient feels perfectly well with a level

Box 3 What to tell patients with newly diagnosed hypothyroidism

- Levothyroxine has a half life of seven days in the bloodstream and it will take a week or more to start to feel better. Conversely, if one tablet is missed out, there will be no noticeable effect
- If muscle weakness, stiffness, or cognitive defects are present these may take up to six months to fully resolve
- Levothyroxine should be taken on an empty stomach to maximise absorption
- Treatment is generally life long and only small changes in levothyroxine dosage are likely over that time, as determined by yearly measurements of thyroid stimulating hormone levels
- In the UK, patients with hypothyroidism are eligible for a medical exemption certificate for prescription charges (FP92)

Box 4 Drugs affecting dosage of levothyroxine

Drugs preventing absorption of levothyroxine

- Calcium salts
- Ferrous sulphate
- Aluminium hydroxide
- Cholestyramine

Drugs increasing clearance of levothyroxine

- Phenytoin
- Carbamazepine
- Phenobarbitone
- Rifampicin

Tips for non-specialists

- It may take several months before symptoms of hypothyroidism are resolved after biochemical correction of hypothyroidism
- If thyroid stimulating hormone level is persistently raised after an adequate dose of levothyroxine, suspect poor compliance (concordance), the presence of drug interference, or malabsorption (for example, undiagnosed coeliac disease)
- If a new drug is started, think whether the drug would interfere with thyroxine absorption or thyroid hormone action; ferrous and calcium salts are common culprits
- Monitoring replacement with serum thyroid stimulating hormone alone is adequate in most patients with hypothyroidism; the important exception being those with pituitary or hypothalamic disease
- Consider referring to a specialist if symptoms do not improve or worsen after treatment with levothyroxine, if serum thyroid stimulating hormone level remains persistently raised while the patient is receiving a full dose of thyroxine, if other morbidity or complications exist (such as active and unstable ischaemic heart disease), or in pregnancy

in the upper half of the reference range, then adjustment is unnecessary. If persistent fatigue, somnolence, or subtle cognitive problems (forgetfulness, befuddlement) exist then it is reasonable to increase the dose by 25 μg daily, or on alternate days. Although an open label non-randomised study has suggested that titrating the dose of levothyroxine upward (often leading to suppression of thyroid stimulating hormone) is associated with improvement in wellbeing,[22] this was not confirmed by a recent randomised control trial.[23] A fully suppressed serum thyroid stimulating hormone level (<0.1 mU/l) should always be avoided.[9] A low level (0.1 to 0.4 mU/l) may be acceptable in a younger person who does not feel fully well while taking a smaller dose of levothyroxine. Low thyroid stimulating hormone levels in older people (>60 years) should trigger a small dose reduction of 25 μg daily, or on alternate days. A meta-analysis has shown that low levels of thyroid stimulating hormone (0.1 to 0.4 mU/l) increase the risk of osteoporosis in over 60s.[24] In addition, a longitudinal observational study has indicated that low thyroid stimulating hormone levels may contribute to a three-fold increased risk of atrial fibrillation.[25]

What are the challenges of levothyroxine replacement?

A persistently abnormal thyroid stimulating hormone level

Patient non-compliance (non-concordance) with levothyroxine therapy can sometimes be a problem. When levothyroxine is taken only on the day of attendance for the blood test this typically results in a chronically raised thyroid stimulating hormone level but normal or raised free thyroxine levels. In many cases reiterating that levothyroxine has a long half life (box 3) is sufficient to persuade the patient to take the tablets regularly, even if they do not feel different on days when the dose is missed. In most people it is safe to recommend that they take a double dose on the day after a missed tablet (exceptions being active ischaemic heart disease and atrial fibrillation). A small randomised controlled crossover trial has shown that giving levothyroxine weekly (seven times the daily dose taken once a week) is a safe regimen[26] and can be used in refractory cases.

Less commonly a persistently raised thyroid stimulating hormone level despite an apparently adequate dose of levothyroxine can be caused by drugs (box 4) or by malabsorption. It is worth excluding coeliac disease (measuring endomyseal or transglutaminase antibodies) and autoimmune gastritis (measuring parietal cell antibodies) in this situation, as observational studies have shown that the two autoimmune conditions coexist with autoimmune hypothyroidism more often than would be expected.[27,28] Rarely, interference to the laboratory assay as a result of heterophil antibodies being present in the patient can lead to artefacts.

Patient does not feel well despite well controlled thyroid stimulating hormone level (0.1 to 2.5 mU/l)

Other diagnoses, both physical and psychological, need to be considered, as mild abnormalities of thyroid function are common and the problem that is making the patient feel unwell might not have been treated. If the patient clearly reports feeling worse while taking levothyroxine, this should suggest Addison's disease.[29] Other autoimmune conditions, particularly pernicious anaemia, may coexist with hypothyroidism and be the dominant cause of non-specific symptoms. People with sleep apnoea may also have non-specific symptoms that are superficially similar to hypothyroidism

Box 5 Selected populations requiring screening for hypothyroidism

- Patients with Down's syndrome and Turner's syndrome
- Patients taking drugs such as amiodarone, lithium, thalidomide, interferons, sunitinib, and rifampicin
- Patients who have received radioiodine treatment or neck radiotherapy
- Patients who have had subtotal thyroidectomy
- Patients with type 1 diabetes and autoimmune Addison's disease

A patient's perspective

At the age of 40 I started feeling tired and was finding it difficult to concentrate in a new job. At first I put it down to pressures at work, but after six months I was feeling quite miserable. I found that I was coming home from work and needed to take a nap before I could face an evening out. It was increasingly difficult even to walk the 100 m up hill to my house, needing to stop several times. I wasn't out of breath, it was just that my muscles ached too much to walk. I was also always feeling cold.

However, it still took me a full nine months before I visited my doctor, who found out after a blood test that I had an underactive thyroid gland and prescribed me levothyroxine. The doctor was surprised that I was still managing to function as my results were so extreme. Within a few days of taking levothyroxine, I was feeling so much better. It was unbelievable!

I remained well for the next 11 years, until I started to feel extremely tired again, and this time I was losing weight. I was diagnosed with type 1 diabetes and am beginning to feel better again on insulin.

Tricia Condliffe, Exeter

Additional educational resources

Resources for healthcare professionals

Roberts CGP, Landenson PW. Hypothyroidism. *Lancet* 2004:363:793-803—An indepth review on the pathogenesis and management of hypothyroidism

Thyroid disease manager (www.thyroidmanager.org/)—An online textbook that includes a comprehensive chapter with up to date references on hypothyroidism

UK guidelines for the use of thyroid function tests (www.british-thyroid-association.org/TFT_guideline_final_version_July_2006.pdf)—Guidelines on thyroid function tests, which include a separate chapter on the investigations and treatment of hypothyroidism

Resources for patients

British Thyroid Foundation (www.btf-thyroid.org/)—Provides general information about different thyroid disorders, patient information leaflets, local patient information meetings, and telephone support

British Thyroid Association (www.british-thyroid-association.org/patient_info.htm)—Has a separate section for information for patients, providing information on various thyroid disorders

American Thyroid Association (www.thyroid.org/patients/patients.html)—Has a separate section for patients, providing patient education brochures, frequently asked questions, recommended list of books for patients and families, update on current thyroid research, and links to other support organisations

Hormone Foundation (www.hormone.org/thyroid/)—Offers information on different thyroid and endocrine disorders, with fact sheets, brochures, patient guides, and up to date patient information articles

(tiredness, weight gain, poor concentration), and these may have triggered testing of thyroid function.

If the thyroid stimulating hormone level is above 1.5 mU/l, a small dosage increment of 25 μg on alternate days should be considered or a change to nocturnal dosing, which may give a subtle increase in absorption.[30] If attempting to refine levothyroxine dosages to achieve wellbeing, in our experience it is worth recommending that the patient keeps to one particular brand of levothyroxine to avoid small differences between formulations that might cause a change in symptoms.

Unanswered questions

Why do some patients with hypothyroidism continue to feel unwell despite taking adequate doses of levothyroxine?

Would a combination of levothyroxine with slow release formulation of triidothyronine have advantages over levothyroxine therapy alone?

Is the vascular risk associated with subclinical hypothyroidism ameliorated by early thyroid hormone replacement?

Are there differences in long term outcome from treating adults with hypothyroidism to different target ranges for serum thyroid stimulating hormone?

Current ongoing clinical trials

Evening versus morning administration of levothyroxine (Medical Centre Rijnmond-Zuid, Netherlands)

Levothyroxine replacement in pregnant women with mild (subclinical) hypothyroidism (University of Cardiff, UK, and National Institute of Child Health and Human Development, USA)

Thyroid hormone dose adjustment in hypothyroid pregnant women (Brigham and Women's Hospital, USA)

Generic versus name brand levothyroxine (Children's Hospital Boston, USA)

Treating hypothyroidism in older patients and those with ischaemic heart disease

Because people with longstanding hypothyroidism may have bradycardia, which can mask substantial but asymptomatic coronary artery disease,[31] levothyroxine should be replaced cautiously in older patients (>60 years) or those with known ischaemic heart disease. Particular attention is required in those with profound and longstanding hypothyroidism (thyroid stimulating hormone level >50 mU/l). In these instances, or in someone with active angina pectoris or recent acute coronary syndrome, the starting dose of levothyroxine should be 12.5 or 25 μg daily, which should then be increased every three to six weeks until euthyroidism is achieved.

Hypothyroidism in pregnancy

Maternal hypothyroidism in pregnancy is associated with adverse obstetric outcomes and long term developmental sequelae. Referral to a specialist is necessary. The management of hypothyroidism in pregnancy has been discussed in detail in a recent review.[32]

Current controversies

Who should be screened for hypothyroidism?

Routine population screening for thyroid disease is controversial. A recent systemic review found insufficient evidence to recommend routine screening of thyroid disease in the general adult population.[33] UK guidelines for the use of thyroid function tests, however, recommend that specific groups of people at high risk of developing hypothyroidism should be offered annual screening (box 5).[8]

Should combined triiodothyronine with levothyroxine be used?

Several studies have examined whether combination therapy of primary hypothyroidism with triiodothyronine and levothyroxine might be helpful. A recent prospective study has, however, shown that normal triiodothyronine levels could be achieved with levothyroxine treatment alone in patients after total thyroidectomy, without the need to take triiodothyronine.[34] A meta-analysis of 11 randomised controlled trials with more than 1000 participants has shown no obvious benefit from combined triiodothyronine and levothyroxine therapy.[35] A major obstacle to evaluation of such combined therapies is that no currently available formulation contains levothyroxine and triiodothyronine with the relative quantities and release kinetics of the human thyroid gland.

How useful is porcine thyroid extract?

Porcine thyroid extract (common brand name Armour thyroid; Forest Pharmaceuticals, USA) has never been compared with levothyroxine treatment in a randomised study. It is substantially more expensive than levothyroxine and of no proved additional benefit.

SUMMARY POINTS

In adults with newly diagnosed hypothyroidism who are under 60 and without ischaemic heart disease it is safe and efficient to start on a full replacement dose of levothyroxine

Levothyroxine replacement dose is related to body mass; a daily dose of about 1.6 µg levothyroxine/kg body mass is adequate replacement for most adults (equivalent to 100 µg daily or 125 µg daily for an average size woman or man, respectively)

Elderly people and those with ischaemic heart disease should start on a small dose of levothyroxine, and the dose increment should be gradual

Current evidence does not support a clinical benefit from the use of a combination of levothyroxine and liothyronine (triiodothyronine) over levothyroxine alone in the treatment of hypothyroidism

When should general practitioners refer?

Most patients with hypothyroidism can be managed successfully in primary care. Referral should, however, be considered in hypothyroid patients whose symptoms do not respond or worsen after treatment with levothyroxine; the serum thyroid stimulating hormone level is persistently raised while taking the full dose of levothyroxine; or if other morbidity or complications exist (for example, active and unstable ischaemic heart disease). Pregnant women with hypothyroidism should also be referred.

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