Hypothyroidism

After diabetes, hypothyroidism is the most common endocrine condition that we diagnose and treat in primary care. Commonly we detect thyroid disease in patients who present with nonspecific symptoms or signs such as fatigue, weight gain, hair loss or subfertility.

Most cases are straightforward but this section of the Handbook considers some of the dilemmas that we face. I have pulled together evidence from a range of sources to try and cover the issues important to us in general practice.

- What TSH value should we aim for?
- When should we treat subclinical hypothyroidism and how should we monitor if we do not treat?
- Is subclinical hypothyroidism associated with heart disease?
- What about hypothyroidism in pregnancy?

Hypothyroidism statistics:

- Annual incidence of primary hypothyroidism is 3.5 per 1000 women and 0.6 per 1000 men in the UK.
- 3% of the UK population are taking long-term thyroid replacement therapy.
- Research suggests that 40–48% of patients are being over or undertreated.
- 2–4% patients with subclinical hypothyroidism will develop overt hypothyroidism each year.

First the basics, covered in a BMJ review (BMJ 2008;337:a801).

Diagnosis

There is no evidence to support population-level screening for hypothyroidism. The most common cause of an underactive thyroid is autoimmune thyroiditis and this causes slow failure of the thyroid gland so symptoms may be insidious and present over years.

Remember that hypothyroidism is an autoimmune disease and may co-exist alongside other autoimmune conditions such as diabetes, Addison's, vitiligo, pernicious anaemia and coeliac, etc.

There are, however, some groups who should have annual screening for hypothyroidism.

- Screen the following patients annually for hypothyroidism by measuring TSH:
  - Down/Turner syndrome.
  - Patients taking lithium, amiodarone, thalidomide, interferons, sunitinib and rifampicin.
  - Patients who have received radiiodine treatment or neck radiotherapy.
  - Patients who have had subtotal thyroidectomy.
  - Patients with type 1 diabetes or Addison’s disease.

Subclinical hypothyroidism

The evidence base for when to treat subclinical hypothyroidism is not well developed and is based on expert consensus. The rationale for treatment is that 2–4% progress to overt hypothyroidism annually and that patients may have symptoms of an underactive thyroid which impair quality of life, even in the presence of normal free T3/T4. Best practice is as follows:
The exception to the above is in pregnancy or in those trying to conceive when subclinical hypothyroidism should always be treated.

**Starting levothyroxine treatment**

Traditionally we have tended to start patients on a low dose of levothyroxine and titrate it up over a period of months. RCT evidence suggests that for the majority of patients this is not necessary and may waste resources.

- For patients aged >60y or with ischaemic heart disease, start levothyroxine at 25–50μg daily and titrate up every 3 to 6 weeks as tolerated.
- For ALL other patients start at full replacement dose. For most this will equate to 1.6 μg/kg/day (approximately 100μg for a 60kg woman and 125μg for a 75kg man).

If you are starting treatment for subclinical hypothyroidism, this article advises starting at a dose close to the full treatment dose on the basis that it is difficult to assess symptom response unless a therapeutic dose has been trialled.

A small Dutch double-blind cross-over study (ArchIntMed 2010;170:1996) demonstrated that night time rather than morning dosing improved TSH suppression and free T4 measurements, but made no difference to subjective wellbeing. It is reasonable to take levothyroxine at night rather than in the morning, especially for individuals who do not eat late at night.

There is no evidence to support the use of combined T3/T4 preparations above the use of levothyroxine alone.

**Monitoring replacement treatment**

If untreated hypothyroidism has been present for a long time, hyperplasia of the TSH-producing cells in the pituitary can result in it taking 3–6 months for the TSH level to return to the reference range, even if full replacement dose levothyroxine is started straight away.

- When adjusting the dose of levothyroxine, check TSH levels every 8–12 weeks.
- Once on a stable dose, annual TSH monitoring is sufficient (QOF requires a check every 12 months).
- Pregnancy, oestrogen use, advancing age and large changes in body weight can affect thyroxine requirements.
- The goal of treatment is to make the patient feel better and this tends to correspond with a TSH in the lower half of the reference range (0.4–2.5 mU/l). If a patient feels perfectly well with TSH between 2.5 and 5 mU/l there is no need to adjust the dosage.
- Low TSH levels (0.1–0.4 mU/l) in those over 60y have been associated with increased risk of atrial fibrillation and osteoporosis and should prompt a small dose reduction.
- A case-control study confirmed that levothyroxine use in older people increased the risk of fractures and that this was dose-dependent (BMJ 2011;342:d2238). Sadly TSH levels were not measured, so this study can’t tell us whether it is the dose of levothyroxine or the effect on TSH that really affects fracture risk. The accompanying editorial agrees careful monitoring is needed in older people but also suggests that perhaps the normal values for TSH may need adjusting upwards, as lower doses (less TSH suppression) may be adequate in older people because of the associated risks described above (BMJ 2011;342:d2250).

If people don’t feel better on levothyroxine, or if they have a persistently elevated TSH, check compliance. The long half life of thyroxine means that patients won’t feel the effect of the odd missed dose, which may lead to more frequent missed doses. For patients who do not have ischaemic heart disease or atrial fibrillation, there is evidence from a small RCT that taking seven times the daily dose just once a week may be safe.
Subclinical hypothyroidism and CHD

An article in the BMJ Uncertainties series (BMJ 2008;337:a834) acknowledged the conflicting evidence as to the benefits of treating this group. Some studies reported symptom improvement, others did not; also whether subclinical hypothyroidism increased cardiovascular mortality remained uncertain.

A large meta-analysis of more than 55 000 patients looking at the association between subclinical hypothyroidism and coronary heart disease and mortality was recently published (JAMA 2010;304:1365). This differed from previous studies as it looked at individual patient data rather than the overall results of the study. They found:

- Overall, there was no difference in coronary heart disease (HR 1.18 (CI 0.99–1.42)), CHD mortality (HR 1.14 (CI 0.99–1.32)) or overall mortality (HR 1.09 (CI 0.96–1.24)) between those with subclinical hypothyroidism and those who were euthyroid.
- Those who had a TSH ≥10 mU/l at presentation had a significantly increased risk of CHD (HR 1.89 (CI 1.28–2.60)) and CHD mortality (HR 1.58 (CI 1.10–2.27)) but no difference in overall mortality.
- These relationships remained when adjusting for age and traditional cardiovascular risk factors.

However, at this time, we do not know whether treating with thyroxine replacement reduces this risk – there have been no randomised studies which look at the important outcomes of CHD events and mortality.

Hypothyroidism in pregnancy

It is important to adequately manage hypothyroidism in pregnancy (BMJ 2007;335:300). There is an increased rate of early and late obstetric complications with both overt and subclinical hypothyroidism, hence the rationale for treating all in this group. Untreated hypothyroidism can also affect the neurodevelopment of the foetus.

Pregnancy can trigger the progression of subclinical hypothyroidism to overt hypothyroidism and can increase levothyroxine requirements.

Adequate treatment of hypothyroidism during pregnancy reduces complication rates.

- Refer women with overt and subclinical hypothyroidism for shared obstetric care.
- Aim for TSH 0.4–2.5 mU/l.
- Increase usual levothyroxine dose by 30% once pregnancy is confirmed.
- Monitor TSH at least once each trimester.
- If hypothyroidism is diagnosed during pregnancy, specialist assessment is advised to aim to correct TSH as quickly as possible.

Should we screen for hypothyroidism in pregnancy?

NICE and the Endocrine Society Guidelines do not recommend routine antenatal screening for hypothyroidism. They recommend ‘case finding in high risk individuals’. However, some researchers have expressed concerns that this approach will miss a substantial number of cases.

Older studies have shown an association between untreated hypothyroidism in pregnancy and reduced IQ performance of offspring. This study (NEJM 2012;336:493):

- randomised 20 000 pregnant women in the UK and Italy to 1st trimester screening or usual care (with a stored serum sample in the usual care group assessed post-delivery).
- Women with raised TSH or low T4 were offered treatment.
- There was no difference in IQ scores between offspring at 3y.
- It did not assess other obstetric outcomes.

The editorial (NEJM 2012;366:562) points out that cut-offs to start treatment reflect very mild hypothyroidism and that levothyroxine was commenced relatively late in pregnancy (median gestational age 13w) which may be too late to obtain maximum benefits.

This study does not support routine antenatal screening for hypothyroidism. However, a further RCT is currently on-going.
Hypothyroidism

- Common in primary care and diagnosed by a raised TSH and low T4.
- Patients with subclinical hypothyroidism and symptoms may benefit from thyroxine replacement, particularly if their TSH >10 mU/l at diagnosis.
- Asymptomatic patients with a raised TSH between 5 and 10 mU/l should have thyroid peroxidase antibodies checked and if positive annual TSH monitoring; if negative monitor every 3 years.
- Most patients can be started on full treatment dose of thyroxine straight away unless they are aged over 60 or they have a history of ischaemic heart disease.
- The goal of treatment is to improve symptoms and for most patients that will be achieved at a TSH between 0.4 and 2.5 mU/l.
- Subclinical hypothyroidism with a TSH >10 mU/l is associated with an increase in CHD and CHD mortality but not overall mortality. We do not know if treating it reduces these important outcomes.
- All pregnant women with hypothyroidism should be referred for shared care.
- A recent imperfect RCT did not support universal antenatal screening for hypothyroidism – it failed to show any difference in offspring IQ at 3y. It did not assess other obstetric outcomes.
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