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Current recommendations in the management of hypothyroidism:

developed from a statement by the British Thyroid Association Executive

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BACKGROUND

Hypothyroidism is present in about 2–5% of the population and is routinely managed in general practice.[1] Uncorrected disease carries significant morbidity and is associated with an increased risk of lipid disorders, cardiovascular disease, osteoporosis, and cognitive dysfunction.[2] Most cases are due to chronic autoimmune thyroiditis, and are followed by destructive treatment of the thyroid gland with radioactive iodine or surgery.[2] The prevalence of spontaneous hypothyroidism rises with age and is 10 times more common in women than in men.[1] In primary hypothyroidism the earliest biochemical abnormality is an increase in serum thyrotropin (TSH) level with normal free T4 (FT4) and free T3 (FT3) concentrations (subclinical hypothyroidism).[2] A proportion of individuals with subclinical hypothyroidism (approximately 2–4% per annum) will progress to overt hypothyroidism (decreased FT4 associated with increased serum TSH).[1] Patients with overt disease typically manifest symptoms and usually benefit from thyroid hormone treatment.

Synthetic levothyroxine (L-T4) remains the treatment of choice for hypothyroidism[2–4] and is prescribed to an estimated 1.5 million people in the UK.[2] It is simple to administer, and within weeks of initiation most patients achieve normal serum TSH levels, and enjoy restored health.[2] However, a proportion of treated patients continue to suffer ill-health even after normalisation of their thyroid hormone levels.[5] Most GPs will be familiar with the patient who is persistently dissatisfied with L-T4 therapy or those for whom a stable euthyroid state appears unachievable. The management of such individuals is challenging and sometimes frustrating for patients and clinicians alike. In addition recent community-based surveys have highlighted a series of pressing concerns including the indiscriminate use of thyroid tests,[6] overdiagnosis, and excessive treatment of patients with mild hypothyroidism,[7] and an inconsistent approach to the management of subclinical disease.[8]

Accordingly a number of international societies have published best-practice guidelines for the management of hypothyroidism.[2–4] In 2015, the Executive Committee of the British Thyroid Association (BTA) summarised the relevant points in existing hypothyroidism guidelines and published an evidence-based statement on the management of primary hypothyroidism.[2] Here we summarise the key points from the guidance that are of particular relevance to the GP.

MAKING THE DIAGNOSIS

The diagnosis of primary hypothyroidism is based on clinical features supported by biochemical evidence of elevated serum TSH and low or normal FT4. Because the symptoms of hypothyroidism overlap with those of a variety of chronic disease states, primary hypothyroidism should not be diagnosed on the basis of symptoms alone in individuals with a normal serum TSH. Such practice may lead to an erroneous label of hypothyroidism in a patient with another condition and will ultimately result in dissatisfaction with L-T4 therapy.

USE OF THE SERUM FT3 TEST

Serum FT3 is not recommended for the diagnosis or monitoring of hypothyroidism as its diagnostic value remains to be ascertained.[4]

TREATING SUBCLINICAL HYPOTHYROIDISM

The decision to treat individuals with subclinical hypothyroidism will depend on the likelihood of progression to overt hypothyroidism together with any potential benefits of reducing adverse effect risk (Box 1). Although the evidence for benefit is inconsistent, treatment is generally advised in patients with positive antibodies or serum TSH >10 mU/L as progression is more

Box 1. Indications for synthetic levothyroxine therapy in subclinical hypothyroidism

- Serum thyrotropin >10 mU/L
- Positive thyroid antibodies
- Pregnant or intending conception
- Symptoms suggestive of hypothyroidism
- Presence of goitre
- Aged <65 years with dyslipidaemia or other cardiovascular risk factors

Box 2. Evaluation of patients on synthetic levothyroxine (L-T4) with persistently raised serum thyrotropin

- Check that the L-T4 dose is appropriate for body weight
- Check and encourage compliance
- Ensure correct administration of L-T4, that is, with water on an empty stomach and at least 30 minutes before breakfast or at bedtime. Check that L-T4 is not being taken with fruit juices, cereal, beverages, or milk
- Check potential interference from medications, for example, antacids, iron compounds, and proton pump inhibitors. These medications should be taken separately from L-T4
- Consider other disease states that interfere with L-T4 absorption including coeliac disease, pernicious anaemia, gastritis, or malabsorption

Box 3. Alternative causes of ill-health in euthyroid individuals treated with synthetic levothyroxine

- Other endocrine or autoimmune conditions, for example, diabetes, Addison's disease, hypopituitarism, or coeliac disease.
- Nutritional deficiency states: iron deficiency anaemia, vitamin B12 deficiency, folate deficiency, or vitamin D deficiency.
- Other causes of fatigue: simple obesity, obstructive sleep apnoea, chronic fatigue syndrome, fibromyalgia, depression and anxiety states, stressful life events, poor sleep patterns, lifestyle-related exhaustion, alcohol excess, or chronic drug usage; for example, beta-blockers, statins, glucocorticoids, opioids, diuretics, and benzodiazepines.

likely in such individuals.[9] Younger persons (<65 years) with cardiovascular risk factors such as dyslipidaemia should also be treated because studies have shown an association between subclinical hypothyroidism and cardiovascular mortality in younger individuals.[9] In addition, it is reasonable to treat patients with goitre or with symptoms suggestive of hypothyroidism. All females with subclinical hypothyroidism who are pregnant or intending conception should also be treated due to the potential risk of adverse pregnancy outcomes.[4] For those patients where treatment is not advised, regular thyroid hormone monitoring should be carried out 6–12-monthly.[9]

INITIATING LEVOTHYROXINE

Daily L-T4 requirement is 0.8–1.6 mcg/kg and starting doses typically vary between 50–125 mcg/day. Treatment should be initiated with full replacement doses except in older people or in individuals with cardiac disease, who require smaller starting doses to avoid inducing cardiac ischaemia.[4]

MONITORING TREATMENT

Treatment should aim for TSH levels within the normal reference range. Once a patient is established on levothyroxine it is recommended that serum TSH is checked annually. Deliberate TSH suppression (serum TSH <0.1 mU/L) with high-dose therapy should be avoided as overtreatment carries a risk of adverse effects especially atrial fibrillation, strokes, and osteoporosis.[2] The exception is in the post-ablative management of patients with thyroid cancer who require a suppressed TSH to reduce cancer recurrence risk.[2] Such targets are decided by the specialist team.

PATIENTS WITH PERSISTENTLY ABNORMAL SERUM TSH LEVELS

Patients with persistently abnormal serum TSH levels should be reviewed to ensure that L-T4 is being administered correctly and that factors which affect L-T4 availability have been addressed (Box 2). Non-adherence is common and should be explored in a non-confrontational manner.

PATIENTS WITH PERSISTENT SYMPTOMS DESPITE NORMAL SERUM TSH

Individuals treated with L-T4 may remain symptomatic despite a normal serum TSH. Such patients should be carefully assessed for other conditions that may account for symptoms (Box 3). Symptom and lifestyle management support should be provided and further L-T4 dose adjustments may be attempted, aiming for a serum TSH at the lower end of the reference range. Specialist referral should be considered if none of these measures resolves the symptoms.

COMBINATION L-T4 AND L-T3 THERAPY

Combined therapy with L-T4 and liothyronine (L-T3) is not routinely recommended.

Evidence from controlled trials has shown no added benefit of combined therapy over L-T4 monotherapy in terms of quality of life, mood, or psychometric measures.[2–4] Although some individuals express a preference for combined therapy, there are limited long-term safety data to support its routine use in practice. Specialist referral should be considered in individuals who have unambiguously not benefited from L-T4 and have been thoroughly evaluated for alternative causes of ill-health. Some endocrinologists will consider a trial of combination therapy in carefully selected patients following an informed discussion of the potential adverse consequences of over-replacement.

OTHER TREATMENTS

There is no evidence to support routine use of thyroid extracts, L-T3 monotherapy, compounded thyroid hormones, iodine-containing preparations, dietary supplementation, and over-the-counter preparations in the management of hypothyroidism.[2–4]

PREGNANCY

Pregnant females deserve special consideration. Thyroid hormones are necessary for optimal obstetric outcomes and in females trying to conceive a mildly increased serum TSH (subclinical hypothyroidism) should be corrected due to the risk of adverse obstetric outcomes associated with thyroid dysfunction, such as miscarriage and low birth weight.[4] Serum TSH reference ranges in pregnancy differ from the general population and trimester-specific serum TSH reference ranges should be used in pregnancy where available. In the absence of such reference values it is recommended that the upper limit of serum TSH is 2.5 mU/L in the first trimester and 3.0 mU/L in subsequent trimesters.[4] Referral to a specialist antenatal clinic is recommended in pregnant females with raised serum TSHs, and depending on local arrangements GPs may need to initiate L-T4 pending specialist review. Typical starting doses in pregnancy are the same as in the general population (50–125 mcg/day) but care must be taken to avoid overtreatment, which may have detrimental obstetric effects. TSH should then be checked every 4–6 weeks initially and then 3-monthly in later pregnancy.

Provenance

Freely submitted; externally peer reviewed.

Competing interests

Onyebuchi Okosieme is conducting research into the genetics of thyroid hormone replacement (GENTHYR Study) funded by Concordia International (formerly AMco), manufacturers of levothyroxine (T4) and liothyronine (T3). Onyebuchi Okosieme and Mark Vanderpump are executives of the British Thyroid Association (BTA) and are co-authors of the BTA statement on hypothyroidism.

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