Subclinical Hypothyroidism

Subclinical hypothyroidism (SCH) is diagnosed when peripheral thyroid hormone levels are within the normal range, but thyroid stimulating hormone (TSH) is mildly elevated.

About 62% of TSH levels between 4 and 10 mIU/L normalise without intervention within five years.[1]

Biochemical measurement

There is biological variation in TSH levels which may rise in response to stress and transient disease. TSH secretion also has a diurnal variation with a peak late at night/early hours of morning. This biological variation in TSH values means that one abnormal TSH level should be followed by a repeat blood test to confirm the diagnosis.

Measurement of serum TSH is generally considered the best screening test for thyroid disease. Increased values indicate hypothyroidism. The test is both sensitive and specific. Serum TSH concentrations have a logarithmic relationship with serum thyroxine, so that a doubling in thyroxine produces a hundredfold change in TSH.

TSH is thus a much more sensitive test. The population reference laboratory normal ranges for thyroxine are set wide compared to the normal individual range, so that a fall in thyroxine levels at the lower end of the range may elevate the TSH above normal. However, its sensitivity causes a dilemma, as some patients are found to have elevated TSH levels, but have normal free thyroxine hormone levels, and may also be asymptomatic. Most of the circulating T3 is generated by peripheral conversion from T4, mainly by the liver, through enzymatic removal of an iodine atom from T4. Very little T3 is produced by the thyroid gland itself.

Reference ranges are usually defined as those into which 95% of the population will fall. They are altered slightly by ethnicity, age and iodine intake, and more substantially by pregnancy. There is, however, some debate regarding the upper limits of the TSH reference range. The high background prevalence of autoimmune thyroid disease as well as the age, iodine status, smoking prevalence and ethnicity of the ‘normal’ population may have raised the ‘normal’ upper limit. In people without these factors the normal upper limit may be lower.

Epidemiology

Subclinical hypothyroidism is a common condition. Prevalence increases with age and is more common in women. Approximately 8% of women (10% of women over 55 years of age) and 3% of men have subclinical hypothyroidism.[2]

In studies restricted to older persons, the reported prevalence of subclinical hypothyroidism is between 1.5-12.5%.[3] Treatment with thyroid hormones is increasing and more than 10-15% of people aged over 80 years are prescribed levothyroxine replacement therapy.

Aetiology

Causes are the same as those of overt thyroid disease:

- Chronic autoimmune thyroiditis - Hashimoto's disease. This is by far the most common cause, accounting for over 90% of cases.
- Treatment of hyperthyroidism - most commonly after radioactive iodine treatment.
- Hypothyroidism can occur in 5-25% of patients treated with surgery or antithyroid drugs.
- Less common causes are medications - eg, lithium or amiodarone.
- Other causes include head and neck surgery or radiotherapy.

Clinical features

The term subclinical is at times inaccurate, as some patients have symptoms. In the elderly a diagnosis of hypothyroidism may be delayed by wrongly attributing the symptoms of, for example, fatigue and constipation to ageing.

Clinical manifestations can be explained by assuming that a T4 level of 6-7 mcg/dL, although inside the normal range, may represent a significant decrease from a previous normal of 10 mcg/dL, and is low for this particular patient.

Some studies have suggested that if symptoms are present then treatment with thyroxine will resolve them.

Common clinical features of hypothyroidism include:

- Depression and fatigue.
- Hyperlipidaemia and hyperhomocysteinaemia.
- Goitre.
- Coarse hair.
- Cold intolerance.
- Constipation and weight gain.
- Hoarseness.
- Hearing loss.
- Menorrhagia.
- Slow return phase in knee reflexes.
- Bradycardia.
- Coronary artery disease or cardiac risk factors.

### Investigations

In The UK, screening is not felt to be warranted although case-finding in women at the menopause or if visiting a doctor with nonspecific symptoms may be justified.

The practical approach may be to measure thyroid function in those patients who have persistent, nonspecific complaints - women in particular, and the elderly.

Borderline results and asymptomatic patients need to be repeated at a consistent time of day, with consistent fasting status.

### Differential diagnosis

There are a few other causes of a raised TSH in the presence of normal thyroxine levels:

- Recovery from acute (non-thyroidal) illness.
- Assay variability.
- Heterophile antibodies interfering with the TSH assay (heterophile antibodies are weak antibodies with multispecific activities, which can cause significant interference immunoassays).
- Central hypothyroidism: in these patients there is hypothalamic or pituitary failure, usually leading to normal or only mildly raised TSH in the presence of low serum T4 and T3, with overt hypothyroidism (but no goitre). It is rare - around 1 in 100,000, and usually associated with other pituitary axis abnormalities. Causes include pituitary microadenoma and pituitary infarction.

### Associated diseases

TSH elevation is important as a risk factor for cardiovascular disease.

Patients with full hypothyroidism have serum levels of triglycerides, total cholesterol and low-density lipoprotein (LDL) cholesterol that are elevated. The same changes exist in subclinical hypothyroidism, but are less marked and less consistent.

### Management

A 2019 review and meta-analysis concluded that almost all adults with SCH would not benefit from treatment with thyroid hormones\(^\text{[1]}\). The review included 21 trials with 2,192 participants. For adults with SCH, thyroid hormones consistently demonstrated no clinically relevant benefits for quality of life or thyroid-related symptoms, including depressive symptoms, fatigue and body mass index (moderate to high quality evidence). Other factors in the strong recommendation include the burden of lifelong management and uncertainty on potential harms.

Instead, clinicians should monitor the progression or resolution of the thyroid dysfunction in these adults.

The recommendation does not apply to women who are trying to become pregnant, or patients with TSH >20 mIU/L.

It may not apply to patients with severe symptoms, or young adults (such as those ≤30 years old).

### Medication

If the decision is made to treat:

- Levothyroxine is the drug of choice as it has a long half-life (seven days) and is partially converted to T3 in the body, resulting in a constant physiological level of both T3 and T4 with a single daily dose.
- Dosing: young start at 50 micrograms od.
- Elderly: start at 12.5 to 25 micrograms od.
- Monitor at 6- to 8-week intervals initially. Once the correct dose has been established, monitoring can be 6- to 12-monthly.
- Aim to lower TSH to mid-normal: 1-3 mIU/L.
- Contra-indications to treatment are osteoporosis and fracture risk.
- Goals for treatment are symptomatic improvement, or TSH normalising.
Prognosis

About 62% of TSH levels between 4 and 10 mIU/L normalise without intervention within five years. About 2-5% of people with SCH develop overt hypothyroidism (OH) - progression to OH is particularly more likely with higher serum TSH levels (especially greater than 10 mIU/L), with positive thyroid autoantibodies (to thyroid peroxidase), and in women. Observational data suggest that SCH is associated with an increased risk of coronary heart disease, heart failure, and cardiovascular mortality, particularly in those with TSH levels >10 mU/L. Such associations were not found for most adults with TSH levels of 5-10 mU/L.

The annual rate of progression from subclinical to overt hypothyroidism has been estimated as about 4% in women with raised TSH and positive anti-thyroid antibodies, 2-4% in those with raised TSH alone, and 1-3% in those with anti-thyroid antibodies alone.

Pregnancy

During the first trimester thyroxine is supplied exclusively by the mother. Fetal production begins at 10-12 weeks of gestation. Thyroxine is important for fetal neural development throughout pregnancy, but particularly so in the first trimester. Maternal hypothyroidism has been associated with learning difficulties in euthyroid children, and with increased fetal loss.

Maternal hypothyroidism in the third trimester may increase the chances of caesarean section and of low birth weight. Thyroxine requirement increases during pregnancy so close monitoring is needed to maintain a normal serum TSH.

Pregnant women with goitre, high anti-thyroid antibody titre, family history of thyroid disease or symptoms suggestive of hypothyroidism, should be screened early in pregnancy, or preferably prior to conception, and treated.

All women with SCH who are planning a pregnancy should be referred to an endocrinology specialist.

- Check TFTs before conception if possible.
- If TFTs are not within the euthyroid range, advise delaying conception, until stabilised on levothyroxine treatment - discuss with an endocrinologist if there is any uncertainty about initiation of treatment or what dose to prescribe while waiting for review.
- Check that the woman understands that her dose of levothyroxine must be adjusted as early as possible in pregnancy to reduce the chance of obstetric and neonatal complications.
- Advise the woman to seek medical advice immediately if pregnancy is suspected or a menstrual period is missed.

If the woman is pregnant:

- Check TFTs immediately once pregnancy is confirmed.
- Discuss urgently with an endocrinologist regarding initiation of, or changes to, dosage of levothyroxine and TFT monitoring while waiting for review - trimester-specific TFT reference ranges may vary locally.

Further reading & references

2. Hypothyroidism; NICE CKS, June 2018 (UK access only)
4. UK Guidelines for the Use of Thyroid Function Tests; British Thyroid Association (2006)
5. Goss SKY, Garla V; Subclinical Hypothyroidism

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