

Subclinical Hypothyroidism Patient

Trusted medical information and support

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Subclinical hypothyroidism, also referred to as mild thyroid failure, is diagnosed when peripheral thyroid hormone levels are within the normal range, but thyroid stimulating hormone (TSH) is mildly elevated. It is common, occurring in 3-8% of the population, and carries a risk of progression to overt hypothyroidism of 2-5% per year. There is no absolute consensus on which patients to treat, although there are some clear recommendations.^{[1][2]}

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.^[3] 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 is 3-8%, increasing with age and being more common in women. After the sixth decade the combined prevalence in both men and women is around 10%. 80% of these patients have a serum TSH of less than 10 mIU/L, and 80% have antithyroid antibodies.^[4]

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.

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

Recommendations about thyroid screening have been inconsistent.

The American Thyroid Association (2001) recommended that adults be screened for thyroid dysfunction by measurement of the serum thyrotropin concentration, beginning at age 35 years and every five years thereafter.

The US Preventive Services Taskforce - slightly more recently (2004) - stated that a case had not been made for routine screening.^[5]

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 in view of the high prevalence of mild and subclinical thyroid failure.

The practical approach may be to measure TSH in those patients who have persistent, nonspecific complaints - women in particular, and the elderly.^[6]

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

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.

Some studies have shown a decrease in LDL and total cholesterol levels after treatment with thyroxine, although others have refuted this.^{[7][8]} A sensitive measure of myocardial contractility, the ratio of pre-ejection period to left ventricular ejection time, has also been shown to improve in patients with subclinical hypothyroidism, treated with levothyroxine, compared with those on placebo.

Management^[2]

If the elevation of TSH level is large and it has been so for a long period of time, anti-thyroid antibodies will also have been present. This situation carries a greater likelihood of progression to overt hypothyroidism and therefore a greater potential benefit from treatment.

When to treat:

- All patients with TSH ≥ 10 , or clinical features of hypothyroidism, should be treated.^{[2][4]}
- All patients who are pregnant, or contemplating pregnancy should be treated to decrease the risk of pregnancy complications and of cognitive impairment in the baby.
- Controversy remains regarding the treatment of non-pregnant adult patients with serum TSH < 10 mIU/L: in this subgroup, treatment should be considered in symptomatic patients, patients with infertility, and patients with goitre or positive anti-thyroid peroxidase (TPO) antibodies.
- Limited evidence suggests that treatment of subclinical hypothyroidism in patients with serum TSH < 10 mIU/L should probably be avoided in those aged > 85 years.

How to treat^{[3][9]}

- 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 a fall in LDL cholesterol, or symptomatic improvement, or TSH normalising. Some clinicians believe that treatment targets should be the lower half of the reference range (below 4.0) but many others (including the National Institute for Health and Care Excellence) continue to feel that achieving a TSH within the reference range (usually < 5.5 , depending on the laboratory) is adequate in an asymptomatic patient. There is no evidence for any benefit to long-term outcomes such as cardiovascular disease through treating to a lower level, and there may be an increased risk of osteoporosis. The exact upper limit of normal for the serum TSH level remains controversial. Lowering it to 3.0 or even 2.5 mIU/L has been proposed. However, many criticise this:
 - The argument for lowering the upper limit of normal is the higher level of antithyroid antibodies detected in persons with a serum TSH level between 3.0 and 5.0 mIU/L and the higher rate of progression to clinical thyroid disease.
 - The argument against lowering the upper limit of normal for TSH values is that large patient numbers would be diagnosed with hypothyroidism without any clinical or therapeutic benefit from this diagnosis.

Complications

- Hypercholesterolaemia
- Coronary artery disease

Prognosis

- Risk of progression to overt hypothyroidism rises with serum TSH level.
- The presence of goitre, elevated thyroglobulin antibodies, coeliac disease, and thyroid peroxidase antibodies, plus higher TSH predict a progression toward overt hypothyroidism.
- Replacement therapy is not recommended in asymptomatic individuals with subclinical hypothyroidism but with TSH 5-10 mIU/L, no goitre, and negative anti-thyroid antibodies.

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.^[10]

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.

Further reading & references

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