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Abnormal thyroid stimulating hormone levels: when and who to treat

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Thyroid stimulating hormone (thyrotropin, TSH) measurement is the most widely used test to determine whether a patient has thyroid dysfunction. There is a negative feedback loop between the thyroid and pituitary so TSH levels represent a tissue response to ambient thyroid hormone levels. When pituitary function is normal, the inverse relationship between serum TSH and free thyroxine (FT4) levels is log/linear: a small increase in FT4 will produce a large decrease in TSH and vice versa. Thus, an abnormal TSH level is a sensitive, but not specific, marker of thyroid dysfunction.

Measurement of thyroid stimulating hormone

Improvements in methodology have increased the sensitivity of TSH measurement, with third-generation assays routinely able to detect levels as low as 0.02 mU/l. Dynamic testing of TSH responses (eg to thyrotropin-releasing hormone) are now redundant.

Abnormal thyroid stimulating hormone

When is the thyroid stimulating hormone abnormal?

Physicians frequently talk about 'normal range' when discussing laboratory values, but biochemists use 'reference range'. The latter term comprises 95% of measurements made on healthy volunteers. 'Reference range' is not only semantically correct but also emphasises that in any test some healthy individuals will have values outside the range. TSH levels within a healthy population are not normally distributed but have a long tail of values towards the upper limit.

Some individuals in the upper half of the reference range may develop hypothyroidism decades later,[1] leading to recent suggestions that the TSH reference range is too wide as it includes individuals who may already have mild thyroid autoimmune damage.[2] However, the reference range of TSH is unchanged when individuals in populations with a normal iodine intake are rigorously screened to exclude any evidence of thyroid autoimmunity.[3] Therefore, current reference ranges for TSH remain around 0.4–4.5 mU/l, with some variation between laboratories depending on the exact assay method used.[4]

Table 1. Causes of raised thyroid stimulating hormone (TSH).

Cause of raised TSH	Free thyroid hormone level
Primary hypothyroidism:	
Overt	↓
Subclinical	N
Poor adherence to levothyroxine replacement	↑, N or ↓
Assay interference (heterophilic antibodies)	N
Non-thyroidal illness (recovery phase)	N or ↓
Some cases of TSH-receptor resistance	N or ↓
Secondary hyperthyroidism:	
Some cases of TSH-secreting adenoma*	↑
Some cases of thyroid hormone resistance**	↑

* TSH is immunoreactive but bioinactive.
** Patients are euthyroid; elevated free thyroid hormone levels compensate for relative resistance.

TSH values do not change significantly through daylight hours and there is no need to take sex or age into account in adults.[5] However, in pregnancy, TSH levels normally fall during the first trimester due to the thyroid-stimulating action of chorionic gonadotropin. Also, some drugs, illnesses and other factors can alter serum TSH levels (Tables 1 and 2) and must be excluded before concluding that an abnormal TSH represents thyroid dysfunction.

Investigations

Many laboratories simultaneously measure TSH and FT4; if only a TSH value is provided, the FT4 level must be measured if there is a newly detected abnormal TSH level.[5,6] If the TSH is low and the FT4 normal, free tri-iodothyronine (FT3) should also be measured as FT3 rises before FT4 in hyperthyroidism. Measurement of thyroid peroxidase antibody levels (TPOAb) is helpful in determining whether the patient has thyroid autoimmunity and in predicting future thyroid dysfunction.

Subclinical thyroid disease

When the TSH is elevated and free T4 low, the patient has primary hypothyroidism and requires levothyroxine treatment. Conversely, if the TSH is low (typically undetectable) and the FT4 (or FT3 in T3-toxicosis) elevated, the patient has thyrotoxicosis and further investigations are necessary to identify the cause and determine the appropriate treatment. However, patients are frequently encountered in whom the TSH is abnormal but FT3 and FT4 levels are both normal. Subclinical hyperthyroidism (low TSH) or subclinical hypothyroidism (high TSH) may both progress to overt or clinical thyroid disease, in which case the need for treatment is clear, but controversy exists regarding the need for treatment in the subclinical phase.

Subclinical hypothyroidism

In all cases in which treatment is contemplated, the persistence of an elevated TSH should be documented on two samples 2–3 months apart; this will help rule out non-thyroidal illness as a cause. Subclinical hypothyroidism affects 4–8% of the population, increasing with age.

Treatment

A joint statement on management in 2004 from the American Association of Clinical Endocrinologists, American Thyroid Association and the Endocrine Society[7] concluded that treatment with levothyroxine is indicated if the TSH is greater than 10 mU/l. At this level, symptoms are more likely and the risk is high of future progression to overt hypothyroidism. For TSH values between the upper limit of the reference range and 10 mU/l, the panel could not find even fair evidence of any adverse effect of subclinical hypothyroidism. Most studies have also failed to show a consistent improvement in neuropsychological function and symptoms when levothyroxine is given.[8] Moreover, some individuals with elevated TSH levels inevitably lie outside a reference range which includes only 95% of the healthy population, and clearly will not have any response to treatment.

On the other hand, about 2% of patients with subclinical hypothyroidism and TSH below 10 mU/l progress to overt hypothyroidism annually, rising to 4% if TPOAbs are also present. This joint management statement was challenged subsequently by several experts who wrote a commentary indicating that there are clinical grounds for treatment because many endocrinologists have direct experience of individual patients who derive symptomatic benefit from treatment.[9] Part of the hesitation in starting levothyroxine is that around 20% of patients may end up overtreated, resulting in subclinical (or,

Table 2. Causes of low thyroid stimulating hormone (TSH).

Cause of low TSH	Free thyroid hormone level
Primary hyperthyroidism:	
Overt	↑
Subclinical	N
Pregnancy, first trimester	N*
Non-thyroidal illness (acute phase)	N or ↓
Overtreatment with levothyroxine	N or ↑
Dopamine, glucocorticoids	N
Secondary hypothyroidism (pituitary disease, congenital TSH deficiency)	↓

* Some patients may develop transient gestational hyperthyroidism leading to hyperemesis gravidarum.

Key Points

Serum thyroid stimulating hormone (TSH) is a sensitive measure of thyroid function, but abnormal TSH does not inevitably imply thyroid dysfunction

Diagnosis of subclinical thyroid dysfunction requires the exclusion of other causes of an abnormal TSH and a sustained TSH abnormality over at least 2–3 months

Levothyroxine treatment is indicated in subclinical hypothyroidism if the TSH is above 10 mU/l; the benefits of treatment are debatable below this level

The commonest cause of raised TSH in patients taking levothyroxine is poor adherence to treatment

Adverse effects from subclinical hyperthyroidism are inversely proportional to the TSH level; treatment should be considered if the TSH is below 0.1 mU/l, especially if there are other risk factors

KEY WORDS: levothyroxine, subclinical hyperthyroidism, subclinical hypothyroidism, thyroid disease, thyroid stimulating hormone level, thyroxine

rarely, clinical) thyrotoxicosis – an iatrogenic state that may have greater potential risk to the patient than subclinical hypothyroidism (see below). It is also important to remember that a TSH value of 10 mU/l as a single cut-off for treatment makes little scientific sense. Reference ranges vary between laboratories and within-assay variation may have a blurring effect on the exact point at which a group is biochemically defined.[4]

At present, therefore, the field remains controversial. There are increasing and reassuring data that any cardiovascular risks from subclinical hypothyroidism with TSH values below 10 mU/l are very low or absent.[10,11] My practice is to give patients in this category a three-month trial of levothyroxine at doses sufficient to bring the TSH into the reference range. Treatment is continued if symptoms improve; if there is no improvement, treatment can be stopped. Annual testing of TSH levels is necessary to ensure identification of any progression.

A common scenario which mimics subclinical hypothyroidism is the patient with established hypothyroidism who is taking levothyroxine and has elevated TSH but normal (or even high) FT4 levels. The most common cause is poor adherence to treatment (Table 3) but reasons such as the development of angina should be sought. Tactful management can usually improve the situation, particularly if the patient is reassured that it is safe and sensible to take any missed tablets: levothyroxine can even be given once a week.

Pregnancy

A different set of considerations apply for women who are or want to become pregnant. The fetus is totally dependent on maternal T4 transferred across the placenta in the first trimester of pregnancy and the fetal thyroid does not become fully functional until mid-pregnancy. Good data show an adverse effect of low maternal T4 levels on fetal brain development, even in those with only subclinical hypothyroidism.[12] All such women should therefore receive levothyroxine and are very likely to require increased doses as pregnancy progresses – women with overt hypothyroidism taking levothyroxine usually require a 25–50% dose increase in the first trimester.

Table 3. Causes of raised thyroid stimulating hormone (TSH) in a patient taking levothyroxine.

- Insufficient levothyroxine
- Malabsorption syndromes, especially coeliac disease
- Drugs
- Impaired absorption of levothyroxine (ferrous sulphate, colestyramine, aluminium hydroxide, lovastatin, calcium supplements)
- Altered levothyroxine metabolism (phenytoin, carbamazepine, rifampicin, hormone replacement therapy, amiodarone)
- Failure to break down tablets (try crushing tablets)
- Testing too early after levothyroxine dose increase (allow 6–8 weeks for TSH to fall)
- Poor adherence to treatment (most common cause)

Subclinical hyperthyroidism

As with subclinical hypothyroidism, it is essential to document a persistently low TSH over several months before considering treatment. The prevalence of subclinical hyperthyroidism depends on the TSH cut-off level used to define the population: for TSH values below 0.1 mU/l, the prevalence is about 0.5%, rising to about 3% for TSH levels below 0.4 mU/l. It is more common in areas of past or present iodine deficiency as this increases the formation of thyroid nodules which can develop autonomous function. Annually, around 5% of patients with subclinical hyperthyroidism due to nodular thyroid disease progress to overt hyperthyroidism. The commonest cause of subclinical hyperthyroidism is exogenous due to overtreatment with levothyroxine (it should properly be called subclinical thyrotoxicosis as the thyroid is clearly not overactive in this state).

Adverse effects of subclinical hyperthyroidism have been reviewed by the same expert panel that drew up recommendations for subclinical hypothyroidism.[7] For TSH values between 0.1 mU/l and the lower limit of the reference range, there was felt to be fair evidence supporting a risk of adverse cardiac effects, but not atrial fibrillation (AF), and no evidence for an adverse effect on bone mineral density (BMD). However, with TSH values below 0.1 mU/l, an increased risk of AF seems established and there is also fair evidence supporting a risk of reduced BMD, especially in postmenopausal women, but insufficient evidence linking this to an increased risk of fracture. The caveats with regard to precise cut-off levels for TSH need to be borne in mind,[4] and many studies have not distinguished between suppressed (<0.1 mU/l) and low TSH levels when looking at adverse effects on health of subclinical hyperthyroidism.

Treatment

So far there have been no long-term trials to assess the benefit of treatment. If the cause is exogenous, current recommendations are to reduce the dose of levothyroxine and bring TSH levels to within the reference range. The exception is when TSH suppression is deliberate in the treatment of thyroid cancer or, less commonly now, goitre. Indeed, there is an increasing move to maintain TSH values in the lower part of the reference range in low-risk thyroid cancer patients.[13] If the cause is endogenous then is no clear indication to treat individuals with TSH levels above 0.1 mU/l, although some clinicians might consider radioiodine (or an antithyroid drug) in postmenopausal women with suggestive symptoms, heart disease or low BMD.[14] For those with TSH levels below 0.1 mU/l, treatment with radioiodine or an antithyroid drug should be considered, especially in the elderly and those with heart disease or low BMD.

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Adrenal insufficiency

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Adrenal insufficiency (AI) is caused by:

- primary adrenal failure due to loss or destruction of the adrenal glands or a block in steroid production (as in congenital adrenal hyperplasia (CAH)) or
- secondary failure (ie impairment of the corticotropic axis in the hypothalamic-pituitary region).

Epidemiology and causes
(Tables 1 and 2)

Five per 10,000 population are affected by AI, three because of hypothalamic-pituitary disease and one each from primary AI and CAH.[1] Suppression of the corticotropic axis due to exogenous glucocorticoid treatment (eg for asthma or rheumatoid arthritis) may affect up to 1% of the UK population and 3% of the elderly. More women than men are affected. Age at manifestation varies but is usually around 20–40 years for autoimmune adrenalitis and 30–60 years in secondary adrenal failure.[1] Most patients suffering from CAH manifest neonatally; AI due to other causes is a rare event in childhood.

Clinical presentation

Adrenal insufficiency represents a continual diagnostic challenge as most signs and symptoms are rather non-specific and may be misleading, resulting in delayed diagnosis. Every second patient is diagnosed only after presentation with an adrenal crisis and most will see more than three doctors prior to diagnosis.

Acute AI (ie life-threatening adrenal crisis) typically presents with severe hypotension or hypovolaemic shock, accompanied by vomiting, nausea, abdominal tension, and in some cases even severe neurological dysfunction including coma. In children, it often

Key Points

Adrenal insufficiency (AI) is either of primary origin, mostly due to autoimmune-mediated destruction of the adrenal gland, or of secondary origin, in most cases caused by tumours located in the hypothalamic-pituitary region affecting the regulatory control of adrenal cortisol release

Common clinical symptoms of AI (fatigue, nausea, weight loss and myalgia) are rather non-specific and may lead to considerable delay in diagnosis. Acute AI is life-threatening and may present with fever, severe hypotension or hypovolaemic shock, abdominal tension and, in some cases, even coma

Diagnostic tests should never delay treatment in cases of suspected acute AI. The short synacthen test is the most suitable tool for establishing the diagnosis of AI; baseline cortisol is of limited value

Therapeutic management of AI always requires cortisol replacement. Monitoring is based on clinical judgment. Mineralocorticoid replacement can be monitored by supine and erect blood pressure, urea and electrolytes, and plasma renin activity. Dehydroepiandrosterone (DHEA) replacement therapy can be a beneficial option, in particular in women with signs of androgen deficiency due to lack of adrenal DHEA production

Recent data indicate significantly impaired well-being, increased rates of disablement, inability to work and mortality. Optimisation of therapeutic strategies in AI are therefore an important target of future research

KEY WORDS: Addison's disease, adrenal insufficiency, aldosterone, cortisol, dehydroepiandrosterone