Subclinical thyroid disease

When should it be treated?

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Subclinical hyperthyroidism and hypothyroidism are common and have been associated with many adverse effects, including cardiovascular disorders, cognitive impairment and reduced quality of life. Treatment decisions are clear if TSH levels are very high or low but should be individualised, taking into account patient factors such as age and comorbidities, for milder perturbations.

Key points

- **Subclinical thyroid dysfunction is defined as an abnormal level of thyroid-stimulating hormone (TSH) in the presence of normal thyroxine and tri-iodothyronine levels.**
- **Both subclinical hyperthyroidism and hypothyroidism have been associated with adverse effects, including cardiovascular disorders, cognitive impairment and reduced quality of life.**
- **Patients with a TSH level below 0.1 mU/L or above 10 mU/L should be treated.**
- **In patients with milder TSH perturbations, the decision to treat is influenced by factors such as patient age, comorbidities and cardiovascular risk.**

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Mild aberrations of thyroid function test results are relatively common and more prevalent than overt clinical or biochemical thyroid dysfunction. The entities subclinical hyperthyroidism (SHyper) and subclinical hypothyroidism (SHypo) are essentially defined biochemically, as an abnormality of serum TSH level associated with 'normal' serum free thyroxine (T4) and tri-iodothyronine (T3) hormone concentrations. In contrast, overt thyroid disease denotes more significant thyroid derangements in which serum T4 or T3 levels are outside their reference ranges. To understand SHyper and SHypo, one must acknowledge that existing definitions and terminologies are themselves inherently fluid. The term 'subclinical' is misleading as it implies an absence of clinical symptoms, which may not be correct in every case.[1]

Two physiological principles are crucial to understanding this spectrum of thyroid diseases. Firstly, TSH secretion is exquisitely sensitive to even minor alterations of T4 level within its normal reference range. Secondly, each individual is likely to have a genetically determined set-point or threshold that governs how the hypothalamic–pituitary–thyroid axis responds to changes in T4 or T3 concentrations.[2] This article reviews the current evidence on the outcomes of subclinical thyroid disease outside of pregnancy and whether there is a rationale for therapeutic intervention.

Subclinical hyperthyroidism

Definition and epidemiology

SHyper is defined exclusively by laboratory criteria: a subnormal serum TSH level and normal levels of T4 and/or T3. SHyper has recently been subclassified according to its severity as:

- grade 1 – a low but detectable TSH level (0.1 to 0.39 mU/L)
- grade 2 – a suppressed TSH level (less than 0.1 mU/L), which is

1. Causes and differential diagnosis of subclinical hyperthyroidism*

Persistent subclinical hyperthyroidism

- Endogenous causes
  - Graves' disease
  - Toxic adenoma
  - Toxic multinodular goitre
- Exogenous causes
  - Excessive thyroid hormone replacement
  - Thyroid hormone suppressive therapy for differentiated thyroid cancer

Transient subclinical hyperthyroidism

- Treatment of overt hyperthyroidism with antithyroid drugs or radioactive iodine
- Subacute thyroiditis, painless/silent thyroiditis, postpartum thyroiditis

Low TSH not due to subclinical hyperthyroidism

- Pituitary or hypothalamic insufficiency (secondary or tertiary hypothyroidism)
- Acute psychiatric disease (e.g. psychosis)
- Drugs
  - Glucocorticoids (high dose)
  - Dopamine
  - Somatostatin analogues
  - Dobutamine
- Iodine-induced hyperthyroidism: amiodarone, radiographic contrast agents
- Severe nonthyroidal illness
- Gestational hyperthyroidism (generally first trimester)

* Adapted from Cooper and Biondi. Lancet 2012; 379: 1142-1154; and Biondi et al. Eur Thyroid J 2015; 4: 149-163.[2,5]

thought to have greater clinical significance than grade 1 SHyper.[3]

SHyper can also be subclassified into two categories according to its cause as:

- exogenous – disease caused intentionally or unintentionally by overtreatment with thyroid hormone
- endogenous – disease caused by the more common conditions associated with thyroid autonomy and unrelated to thyroid hormone administration.[2]

Exogenous forms of SHyper are more prevalent than endogenous forms, with SHyper occurring in 20 to 40% of patients prescribed thyroid hormone.[4] The prevalence of SHyper varies with age, sex, race, sensitivity of the TSH assay used and iodine intake.[2,4,5] The US National Health and Nutrition Examination Survey (NHANES) quoted a prevalence of 0.7% of individuals with a suppressed TSH level (less than 0.1 mU/L), after excluding those with known thyroid disease.[6] Another 1.8% of people had a low but detectable TSH level (0.1 to 0.4 mU/L). Studies have also reported a higher prevalence of SHyper in women and a rising frequency with age.[7] Surprisingly, the prevalence of SHyper is higher in iodine-deficient areas because iodine deficiency is thought to induce thyroid autonomy via persistent TSH stimulation.[8]

Aetiology and diagnostic approach to subclinical hyperthyroidism

The causes and differential diagnosis of SHyper are listed in Box 1.[2,5] The first step in the assessment of a patient with suspected SHyper is serum TSH measurement, which is the most sensitive test for diagnosis. Typically, serum T4 and T3 levels are then measured and are often found to be in the high-normal range. This helps rule out overt hyperthyroidism, in which the T3 level is relatively more elevated than the T4 level, reflecting excessive thyroidal production of T3.

After obtaining these laboratory measurements, clinicians should consider potential confounding factors. For example, common conditions that alter thyroid physiology include pregnancy, acute intercurrent illness and various drugs. An increase in human chorionic gonadotropin concentration can lead to low serum TSH concentrations (due to structural homology of the two molecules), found in 18% of pregnant women during early pregnancy, most of whom have a normal serum T4 level.[9] Similarly, in nonthyroidal illness ('sick euthyroid' syndrome) a low TSH level may be followed by a low T3 level because of an increase in conversion of T4 to reverse T3 (an isomer of T3). Generally, these biochemical alterations resolve within weeks of recovery from the acute illness. In addition, commonly prescribed drugs such as glucocorticoids lead to suppression of TSH, illustrating the importance of a thorough medication history.

Furthermore, laboratory assay artefact is under-recognised in commonly used TSH and thyroid hormone immunoassays.[5] For example, human anti-animal or heterophile antibodies can block TSH binding to the capture or detection antibody causing a falsely low TSH level and apparent SHyper. A sensible approach may be to repeat the tests using a different assay platform or to ask the laboratory to check the sample for interference if there are inconsistencies.

It is important to note that a low serum TSH level may occur in healthy elderly people, people of African-American descent and some people who smoke. This is thought to be due to differences in the set-point of the hypothalamic–pituitary–thyroid axis.[3] Commentators have highlighted several limitations of TSH reference ranges and criticised current guidelines for not proposing age-specific reference ranges.[1] Use of age-specific ranges might help to mitigate overdiagnosis and overtreatment of SHyper in certain subgroups.

Patients diagnosed initially with SHyper should be retested within three to six months to determine whether the abnormality is transient or persistent.[3,5] Patients with transient low TSH levels that spontaneously resolve without intervention are thought to have had thyroiditis or Graves' disease and more often have an initial TSH level greater than 0.05 mU/L.[10] Repeat testing is also useful to confirm whether initial results were confounded by an intercurrent illness.

The strongest predictor of progression to overt hyperthyroidism over time is complete suppression of TSH at baseline (TSH level less

than 0.1 mU/L – grade 2 SHyper), with progression occurring in 5 to 8% of patients annually.[7,11] In contrast, Grade 1 SHyper progresses to overt hyperthyroidism in only 0.5 to 0.7% of patients over seven years.[7] The odds of progression are also influenced by the underlying disease. Graves' disease, which is the most common cause of SHyper in younger patients, has a less predictable disease course, with TSH suppression likely to either normalise or progress to overt disease. Toxic adenoma and toxic multinodular goitre are more common causes of SHyper in the elderly. In patients with these conditions, SHyper is more likely to persist over time.[12] Persistent grade 1 SHyper without progression or symptoms in older individuals is commonly due to nodule autonomy and should prompt further imaging studies.

When persistent SHyper is confirmed, the next step should be to determine the aetiology. Thyroid scintigraphy can help to differentiate between Graves' disease (normal diffuse or high uptake), toxic adenoma or toxic multinodular goitre (warm/hot focal uptake) and thyroiditis (low or absent uptake). Exogenous iodine load or exogenous thyroid hormone administration will also lead to low or absent uptake, and an elevated spot urine iodine concentration can help to confirm this. Ultrasonography with colour flow Doppler can help to determine thyroid size, echogenicity, vascularity and the presence of nodules.[5] TSH receptor antibody positivity is also useful to identify autoimmune SHyper (i.e. Graves' disease).

Sequelae of subclinical hyperthyroidism

Endogenous SHyper has been associated with adverse cardiovascular and skeletal outcomes in some studies.

Cardiovascular disease and mortality

Thyroid hormones have well recognised effects on the cardiovascular system. There is evidence linking cardiovascular disorders with changes in thyroid hormone levels even within the reference range, highlighting the sensitivity of this system to subtle changes in thyroid status. Studies have shown an increase in mean and nocturnal heart rate and increased frequency of atrial and ventricular premature beats with SHyper.[4] Associations with heart failure and changes in left ventricular mass, systolic and diastolic function are less well established. Inconsistent results may be attributable to variation in age, degree of TSH suppression and duration and cause of SHyper.

The evidence linking SHyper with atrial fibrillation (AF) has evolved. One study in subjects aged over 60 years showed a 3.1 fold increase in relative risk of AF after 10 years in those with TSH suppression (level less than 0.1 mU/L) at the outset.[13] A meta-analysis showed incident AF was higher in participants with SHyper than in euthyroid subjects but also higher in those with grade 2 compared with grade 1 SHyper over eight years of follow up.[14] Similarly, recent data from the Rotterdam study showed an increased risk of AF with higher T4 levels within the normal range, especially in subjects aged under 65 years.[15] Based on these data, it may be more logical to consider thyroid hormone levels as a continuum of risk rather than adhering to arbitrary definitions of normal and abnormal.[1]

A recent systematic review did not support an increased risk of stroke in SHyper patients despite previous studies suggesting an increased risk of carotid artery plaques.[2] Data from available prospective cohort studies demonstrate a link between SHyper and all-cause mortality and cardiovascular mortality. The latter is particularly increased in people with grade 2 SHyper, men, elderly patients with elevated free T4 levels and those with existing heart disease.[14]

Skeletal system changes

Thyroid hormone stimulates bone resorption by directly upregulating osteoclast function. Overt hyperthyroidism is associated with increased bone turnover, risk of osteoporosis and fracture. Postmenopausal women with SHyper may have increased fracture rates even with TSH levels only in the low range (0.1 to 0.4 mU/L).[16] However, in premenopausal women, most studies show that endogenous SHyper does not affect bone mineral density (BMD). Prospective studies have linked SHyper with an increased risk of hip and nonspine fractures, more pronounced for those with grade 2 SHyper and endogenous SHyper.[17] There appears to be a correlation between the TSH level, duration of subnormal TSH level and risk of osteoporotic fractures in relation to age and sex.[5] For patients receiving thyroxine replacement therapy, only a suppressed TSH level (less than 0.1 mU/L – grade 2 SHyper) increased the risk of fracture.[18]

Symptoms, quality of life and cognitive function

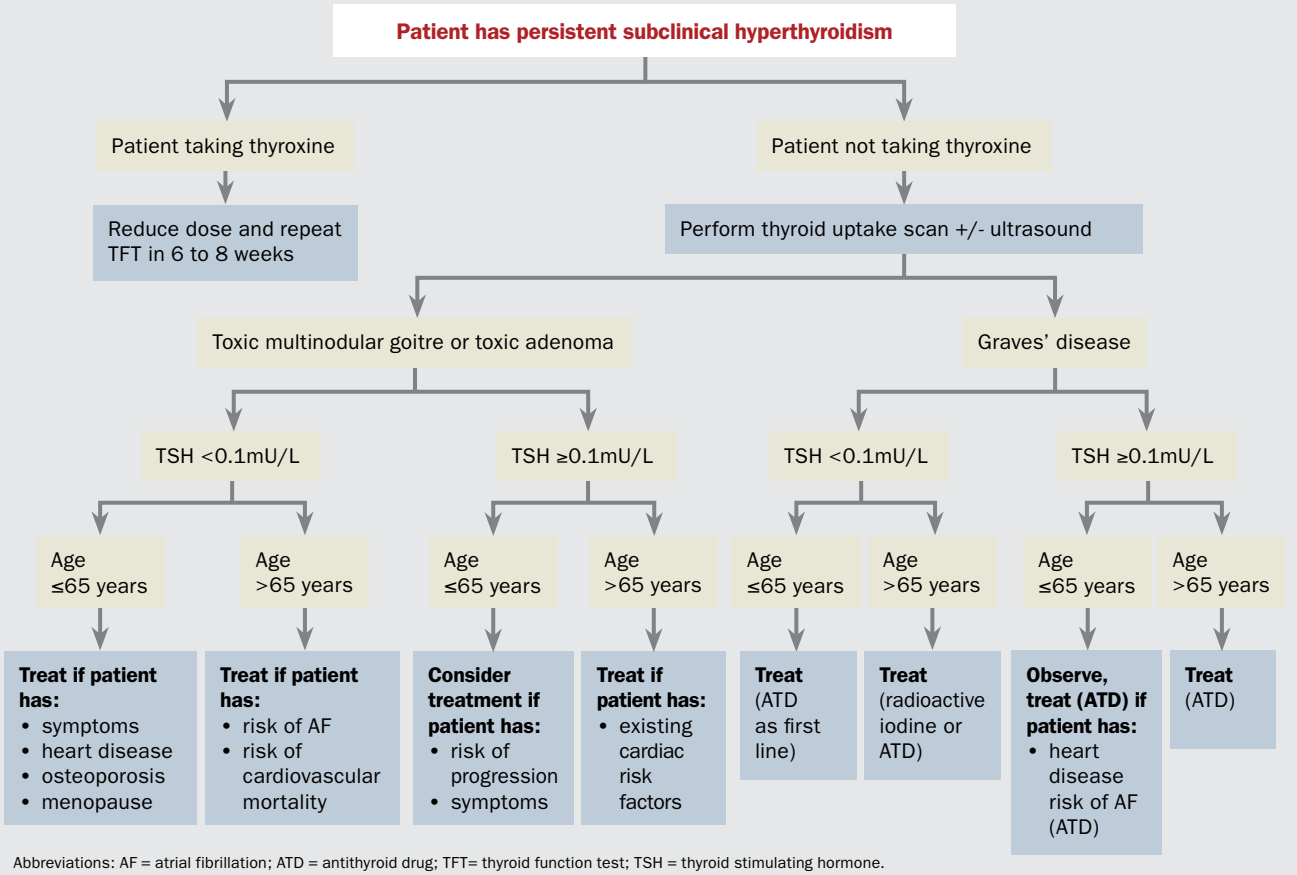
SHyper may be associated with symptoms and signs of thyroid hormone excess, such as palpitations, tremor, heat intolerance, anxiety and reduced exercise tolerance. Impaired quality of life relating to both physical and mental parameters has also been described, particularly in younger patients with grade 2 SHyper.[5] Cardiovascular symptoms are the most specific indicators of mild thyroid hormone excess in the elderly, in whom symptoms can often be masked.[19] Recent studies have described an association between SHyper and dementia or cognitive impairment, although the data remain conflicting and the mechanism has not been elucidated.

When to treat subclinical hyperthyroidism

An algorithm summarising our treatment recommendations for SHyper is shown in Flowchart 1 and is consistent with recent US and European guidelines.[3,5] There are few prospective randomised studies that confirm the risks or benefits of treating SHyper, and the recommendations for treatment are largely derived from the established impact of overt hyperthyroidism on the endpoints discussed above.[20] No controlled intervention studies have been undertaken to confirm a positive effect of TSH normalisation on cardiac endpoints, fracture risk or quality of life.

Treatment of Grade 2 SHyper is strongly recommended in patients aged over 65 years to avoid the risks of progression to overt hyperthyroidism and associations with increased mortality, cardiovascular mortality, incident AF and fractures. Guidelines indicate that treatment of grade 1 SHyper is reasonable even in

1. AN ALGORITHM FOR INVESTIGATION AND TREATMENT OF PATIENTS WITH SUBCLINICAL HYPERTHYROIDISM



Abbreviations: AF = atrial fibrillation; ATD = antithyroid drug; TFT= thyroid function test; TSH = thyroid stimulating hormone.

asymptomatic individuals aged over 65 years if they have existing cardiometabolic risk factors, such as heart disease, diabetes, previous stroke or renal failure.[3, 5] It is important to emphasise that this is not based on data from controlled trials, and that prevention of AF remains a questionable indication for treatment in this subgroup. Studies in postmenopausal women with SHyper found an improvement in BMD after treatment with antithyroid drugs or radioactive iodine but do not confirm that this translates into reduced fracture risk.[21]

Treatment is advised for patients aged less than 65 years with grade 2 SHyper if they have persistent disease and/or symptoms of thyroid hormone excess. Those with endogenous SHyper are likely to benefit from improved quality of life and reduced likelihood of disease progression.[22] There is also a lower threshold for treating this group if they have existing cardiac risk factors.[5] Younger asymptomatic patients with grade 1 SHyper can be monitored without treatment because of the lack of evidence of adverse outcomes and low probability of progression.

The treatment modalities chosen depend on the aetiology of SHyper and are akin to those used in overt hypothyroidism. For example, antithyroid drugs should generally be used first line in Graves' disease at any age if tolerated, as remission can be achieved in 40 to 50% of patients after 12 to 18 months of treatment.[3] Ultimately, the goal of therapy should be to render the patient clinically and biochemically euthyroid.

Subclinical hypothyroidism

Definition and epidemiology

SHypo is defined biochemically as an increased serum TSH level (greater than 4.0 mU/L), with T4 and T3 levels within the normal reference ranges. SHypo can be further characterised as:[23]

- mild – TSH 4.0 to 10 mU/L
- severe – TSH greater than 10 mU/L.

About 75% of patients with SHypo have mild disease, and most are diagnosed on investigation of nonspecific symptoms such as fatigue or weight gain.[2] The prevalence of SHypo is 5 to 10%, with a higher predisposition in women, people of European background and iodine-sufficient populations.[23] There is also a correlation of higher TSH values with advancing age and obesity that does not reflect endogenous thyroid hormone deficiency.[1]

Aetiology and natural history of subclinical hypothyroidism

The causes of SHypo are summarised in Box 2.[2,4,23] Persistent disease can be confirmed by repeat testing after a two to three-month interval, ensuring complete resolution of any acute illnesses. This can help to rule out transient TSH elevations due to drugs or thyroiditis. The presence in the patient's serum of human anti-animal or heterophile antibodies that cross link the capture and detection antibodies in the TSH immunoassay can lead to positive interference and hence falsely elevate the TSH level.

Most cases of persistent SHypo are due to autoimmune thyroiditis or Hashimoto's disease.[4] This is marked by the presence of circulating antithyroid peroxidase antibodies (TPOAb) and/or antithyroglobulin antibodies in 80% of cases.[24] A hypoechoic or heterogeneous echotexture of the thyroid on ultrasound examination may precede antibody detection and provide evidence for autoimmunity, although ultrasound examination is rarely required in this setting. Progression to overt hypothyroidism is more rapid in TPOAb-positive patients with a TSH level above 6 mU/L (4.3% per year) compared with TPOAb-negative patients with a raised TSH level (2.6% per year) and with TPOAb-positive patients with a normal TSH level (2.1% per year).[25] Other predictors of progression to overt hypothyroidism include female sex and TSH level over 10 mU/L.

Sequelae of subclinical hypothyroidism

Symptoms, quality of life and cognitive function

The symptoms of hypothyroidism are not sensitive or specific, and very few patients with mild biochemical SHypo have hypothyroid symptoms. A meta-analysis of seven randomised controlled trials (RCTs) showed that on average there was no evidence of improvement in symptoms such as fatigue after thyroxine initiation.[26] Studies of women aged between 18 and 75 years also showed no correlation of SHypo with reduced wellbeing or quality of life.[27]

Results are conflicting with regard to the association of SHypo with depression or cognitive impairment. People with a TSH level of 3.5 to 10 mU/L did not have any baseline differences in either domain nor any significant response to titrated thyroxine replacement.[23] One study reported that SHypo did not impact on cognitive impairment or depressive symptoms regardless of age but in fact was protective against dependence in activities of daily living in people aged 85 years or older.[19]

Cardiovascular risk and dyslipidaemia

SHypo has been associated with left ventricular diastolic dysfunction and reduced resting and exertional systolic function. This can lead to reduced exercise tolerance. Increased vascular stiffness and endothelial dysfunction have also been described. There is a body of evidence favouring an increased risk of heart failure onset and progression with SHypo but generally for people with TSH values greater than 10 mU/L.[28] SHypo has also been linked with increased mortality in hospitalised patients with heart failure.[29] Cohort studies examining the link between SHypo and ischaemic heart disease have been inconsistent. A large meta-analysis including 50,000 participants showed an increased risk of mortality from ischaemic heart disease in those with TSH levels over 7 mU/L and more coronary heart disease events in those with TSH levels over 10 mU/L.[30] However, age is an important caveat in interpretation of these data because the negative impact on cardiovascular risk appears to be lost in patients aged over 85 years, in whom SHypo may even be protective at TSH levels less than 10 mU/L.[19]

The relationship between overt hypothyroidism and dyslipidaemia, particularly raised total and LDL cholesterol levels, is well established. Observational studies suggest a link between SHypo and total cholesterol and LDL levels that is more pronounced in women and proportional to age and degree of TSH elevation.[23]

2. Causes of subclinical hypothyroidism*

Persistent subclinical hypothyroidism

- Chronic autoimmune thyroiditis (Hashimoto's disease)
- Thyroid surgery (total or partial thyroidectomy)
- Radioactive iodine treatment for hyperthyroidism
- Antithyroid drugs
- Radiotherapy to the head and neck
- Thyroxine treatment – insufficient dosing, noncompliance, drug interaction
- Thyroiditis – postpartum, subacute or painless
- Drugs: amiodarone, lithium, iodinated contrast, interferon, immune checkpoint inhibitors (e.g. pembrolizumab)
- Thyroid dysgenesis
- Iodine deficiency

Physiological or transient TSH elevation

- Nonthyroidal illness (sick euthyroid syndrome) – recovery phase
- Thyroiditis – subacute, painless or postpartum

Elevated TSH not due to subclinical hypothyroidism

- Laboratory assay problem (e.g. heterophile antibody, inactive TSH isoforms)
- Elderly age
- Obesity
- TSH-secreting pituitary adenoma
- Isolated pituitary resistance to thyroid hormone
- Renal impairment
- Adrenal insufficiency (untreated)
- Higher set-point for individual

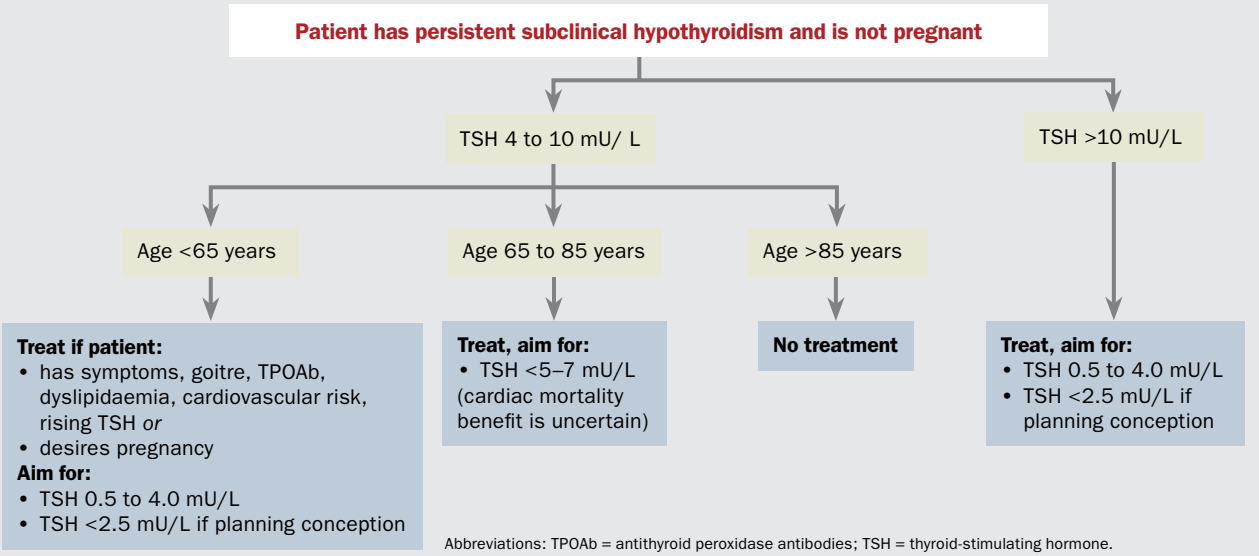
Abbreviations: TSH = thyroid-stimulating hormone.

* Adapted from Cooper and Biondi. Lancet 2012; 379: 1142-1154; Biondi et al. Eur Thyroid J 2015; 4: 149-163; and Pearce et al. Eur Thyroid J 2013; 2: 215-228.[2,5,23]

When to treat subclinical hypothyroidism

An algorithm for the treatment of patients with SHypo (excluding pregnant women) is shown in Flowchart 2. These recommendations are based on the authors' clinical experience and interpretation of the current literature and are similar to those of the European Thyroid Association guidelines.[23] The clearer association between serum TSH level over 10 mU/L and adverse outcomes, such as progression to overt hypothyroidism, dyslipidaemia, cardiovascular disease and mortality, has led to a general consensus supporting treatment in

2. AN ALGORITHM FOR TREATMENT OF NONPREGNANT PATIENTS WITH SUBCLINICAL HYPOTHYROIDISM



Abbreviations: TPOAb = antithyroid peroxidase antibodies; TSH = thyroid-stimulating hormone.

this group regardless of age or symptoms. A few double-blind placebo-controlled trials have concurred that L-thyroxine replacement improves surrogate indexes of cardiac function such as systolic and diastolic function and endothelial function.[2] Indirect evidence from the Cardiovascular Health Study and Whickham Survey suggests a significantly reduced risk of heart failure and all-cause mortality, respectively, in treated patients compared with those untreated.[31,32] Several RCTs have documented a beneficial effect of L-thyroxine on lipid profile, with a meta-analysis of 13 studies showing a reduction in total cholesterol level by 0.2 mmol/L and in LDL level by 0.3 mmol/L.[33]

Given the weak association between SHypo and mood, mental function, symptoms or quality of life, L-thyroxine therapy offers little benefit for these endpoints unless serum TSH level is over 10 mU/L.[2] Studies addressing this issue are heterogeneous regarding patient characteristics, degree of thyroid hormone deficiency and whether euthyroidism was achieved. In symptomatic patients younger than 65 to 70 years with a TSH level less than 10 mU/L, a short-term trial of L-thyroxine may be warranted, with assessment of response after three months.[23] The European guidelines refer to several studies documenting an association between increased TSH levels and thyroid malignancy in patients with thyroid nodules confirmed by histological examination. However, no prospective studies have proven that L-thyroxine therapy can prevent thyroid cancer in this setting.[23]

For patients with TSH levels in the range 4 to 10 mU/L, the decision to start L-thyroxine therapy should be individualised depending on age (favoured in younger individuals), associated medical conditions (particularly cardiac risk factors), the degree of TSH elevation and its persistence, presence of thyroid autoantibodies or existing goitre.[24] The harmful effects of milder SHypo (TSH less than 10 mU/L) on cardiovascular outcomes are less evident in older patients (age 65 to 75 years) and may in fact disappear completely in those aged over 85 years. Hence it seems prudent to adopt a more conservative 'watch and wait' approach in these patients with regard to thyroid hormone replacement.[19]

If a decision is made to start treatment with L-thyroxine then the dose required for SHypo is generally lower than that required in overt hypothyroidism. A daily dose of 25 to 75 µg of L-thyroxine could be considered depending on the TSH level and the presence of existing cardiac disease.[34] Serum TSH should be rechecked four to eight weeks after commencement of L-thyroxine, with higher targets (e.g. up to 5 to 7 mU/L) being suitable for elderly patients.[3,23]

Conclusion

Subclinical thyroid dysfunction is a commonly encountered clinical challenge. It is frequently detected in people with no symptoms, most of whom do not require treatment. For nonpregnant patients, guidelines provide relatively clear recommendations for the more severe cases (e.g. TSH level less than 0.1 mU/L or over 10 mU/L). For milder derangements in thyroid function, treatment decisions must be individualised according to patient characteristics such as age and comorbidities. Despite growing evidence of associations between subclinical thyroid disease and adverse health outcomes, RCTs are needed to help determine whether restoring euthyroidism improves key outcomes. **ET**

References

A list of references is included in the website version (www.endocrinologytoday.com.au) of this article.

COMPETING INTERESTS: None.

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