Subclinical thyroid disease

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Subclinical thyroid diseases—subclinical hyperthyroidism and subclinical hypothyroidism—are common clinical entities that encompass mild degrees of thyroid dysfunction. The clinical significance of mild thyroid overactivity and underactivity is uncertain, which has led to controversy over the appropriateness of diagnostic testing and possible treatment. In this Seminar, we discuss the definition, epidemiology, differential diagnoses, risks of progression to overt thyroid disease, potential effects on various health outcomes, and management of subclinical hyperthyroidism and subclinical hypothyroidism. Treatment recommendations are based on the degree to which thyroid-stimulating hormone concentrations have deviated from normal and underlying comorbidities. Large-scale randomised trials are urgently needed to inform how to best care for individuals with subclinical thyroid disease.

Introduction

The term subclinical denotes the presence of a disease without obvious symptoms, which means that evolution of the disease might be at an early stage.[1] Subclinical has been applied to many medical situations (eg, subclinical cardiovascular disease and subclinical Lyme disease), but subclinical thyroid disease is perhaps the most familiar. Subclinical thyroid disease is defined biochemically: subclinical hyperthyroidism occurs when serum thyroid-stimulating hormone (TSH) concentrations are low or undetectable but free thyroxine (T4) and tri-iodothyronine (T3) concentrations are normal, and subclinical hypothyroidism occurs when serum TSH concentrations are raised and serum thyroid hormone concentrations are normal. By contrast, overt thyroid dysfunction describes more severe thyroid derangements, in which serum concentrations of free T4 or T3 are outside of their reference ranges.

Diagnosis of subclinical thyroid disease is based on the exquisite sensitivity of the hypothalamic-pituitary-thyroid axis. Serum TSH secretion changes logarithmically with arithmetic changes in serum concentrations of free T4. Therefore, alterations in serum free T4 that are within the normal range will cause increases or decreases in serum TSH that are likely to be outside its reference range (figure 1). An important corollary to this concept is that each individual seems to have a specific set point for the hypothalamic-pituitary-thyroid axis,[2] which is, to a large extent, genetically determined.[3,4]

In this Seminar, we present the epidemiology, causes, diagnosis, and management of each disorder, including specific therapies, when indicated. We also discuss issues of controversy, especially in screening and treatment, and we review clinical practice guidelines.

Subclinical hyperthyroidism

Disease forms

Subclinical hyperthyroidism is a form of hyperthyroidism, such that as TSH progressively decreases indicating worsening thyroid overactivity, the probability of clinically significant consequences increases. Subclinical hyperthyroidism can be divided into two categories: exogenous disease caused intentionally or unintentionally by thyroid hormone therapy, and endogenous disease caused by conditions responsible for most forms of overt hyperthyroidism (panel 1). Exogenous subclinical hyperthyroidism is more common than the endogenous form because of the widespread use of thyroid hormone both to treat hypothyroidism and to provide suppressive therapy in patients with non-toxic multinodular goitres and thyroid cancer. 20–40% of patients taking thyroid hormone have a low serum TSH concentration.[5,6] Exogenous subclinical hyperthyroidism is often iatrogenic and reversible by reduction of the levothyroxine dose, so this Seminar focuses on the endogenous form. However, exogenous subclinical hyperthyroidism can cause the same deleterious effects that are seen with endogenous disease.[7,8]

Epidemiology

The population prevalence of subclinical hyperthyroidism is dependent on age, sex, and iodine intake. In the US National Health and Nutrition Examination Survey (NHANES), 0·7% of people had serum TSH of less than 0·1 mU/L (after exclusion of those with known thyroid disease or goitre).[9] In the same dataset, 1·8% of individuals had serum TSH concentrations of less than 0·4 mU/L, which was the lower limit of the reference range. In another population-based study, 0·6% of the population had subclinical hyperthyroidism, of whom about 75% had serum TSH of 0·1–0·4 mU/L and the remainder had concentrations of less than 0·1 mU/L.[10] Findings of other studies have also shown that mild subclinical

Search strategy and selection criteria

We searched Medline for reports published from January, 2000, to December, 2010, with the search terms "subclinical hyperthyroidism" and "subclinical hypothyroidism". The search was restricted to reports published in English, but included translated articles. We supplemented the search with records from personal files and references of relevant articles and textbooks. We focused on reports published since 2006, the few clinical trials that have been done, and population-based studies, but reports published before 2006 were also incorporated when more recent information was not available. Three references were added in November, 2011.

hyperthyroidism (ie, serum TSH 0·1–0·4 mU/L) is more common in the population than is the condition with completely suppressed serum TSH concentrations.[11] The frequency of subclinical hyperthyroidism increases with age, especially in women.[9,10]

By contrast, prevalence of subclinical hyperthyroidism seems to be far higher in iodine-deficient populations. In one survey of elderly individuals living in Iceland (iodine sufficient) and Jutland, Denmark (iodine deficient), less than 1% of Icelandic individuals had low serum TSH (<0·4 mU/L) compared with 9·8% of Danish people.[12] Iodine deficiency might lead to thyroidal autonomy and hyperthyroidism through persistent thyroidal TSH stimulation, with the development of activating mutations in the thyroid follicular epithelium.[13]

Diagnosis

Subclinical hyperthyroidism occurs when the serum TSH is below the lower limit of the reference range and the free T4 and T3 concentrations are normal. Occasionally, patients with low serum TSH and normal free T4 and total T3, but raised free T3 qualify for the diagnosis of overt hyperthyroidism.[14] However, not every person with a low serum TSH has hyperthyroidism (panel 1). Some healthy elderly people might have low serum TSH without identifiable thyroid disease.[15] In these individuals, a low serum TSH might be due to a change in the set point of the hypothalamic-pituitary-thyroid axis with ageing. Serum TSH concentrations tend to be lower in black people than in white people: in NHANES, 4·0% of black people had serum TSH of less than 0·4 mU/L compared with 1·4% of white people (p<0·01).[9] Many black individuals with subnormal serum TSH concentrations are probably in a euthyroid state, and are likely to be given a diagnosis of subclinical hyperthyroidism if the population reference range is used. Low serum TSH concentrations are also seen in some healthy cigarette smokers.[16]

Low serum TSH values are often transitory.[17] In a study from Israel, 51·5% of people with serum TSH of less than 0·35 mU/L had normal serum TSH when retested across a 5-year follow-up.[18] Many patients whose serum TSH concentrations reverted to normal probably had transient episodes of thyroiditis or mild Graves' disease. Although serum TSH concentrations might return to normal spontaneously, some patients develop overt hyperthyroidism with time. The progression rate varies across studies, and is raised in people with completely suppressed baseline serum TSH concentrations[10,19–21] (figure 2). The odds of progression might relate to the underlying disease; TSH supression in patients with Graves' disease is more likely to return to normal, whereas subclinical hyperthyroidism in patients with solitary autonomous nodules and multinodular goitres is likely to persist or progress.[22]

Graves' disease is the most common cause of subclinical hyperthyroidism in young patients, whereas toxic multinodular goitre and solitary autonomous nodules become more common causes with ageing (panel 1).[23] Furthermore, multinodular goitre is more typically associated with subclinical hyperthyroidism than is Graves' disease. In a study of patients with hyperthyroidism who were older than 55 years, hyperthyroidism was subclinical in most patients with toxic multinodular goitre (57%) but in fewer than 10% of those with Graves' disease.[24] Transient or persistent subclinical disease is often seen in patients with overt hyperthyroidism after treatment with antithyroid drugs or radioiodine, and might occur as part of the triphasic course of various forms of thyroiditis (panel 1).

In some cases, low serum TSH concentrations are not indicative of subclinical hyperthyroidism (panel 1). Low

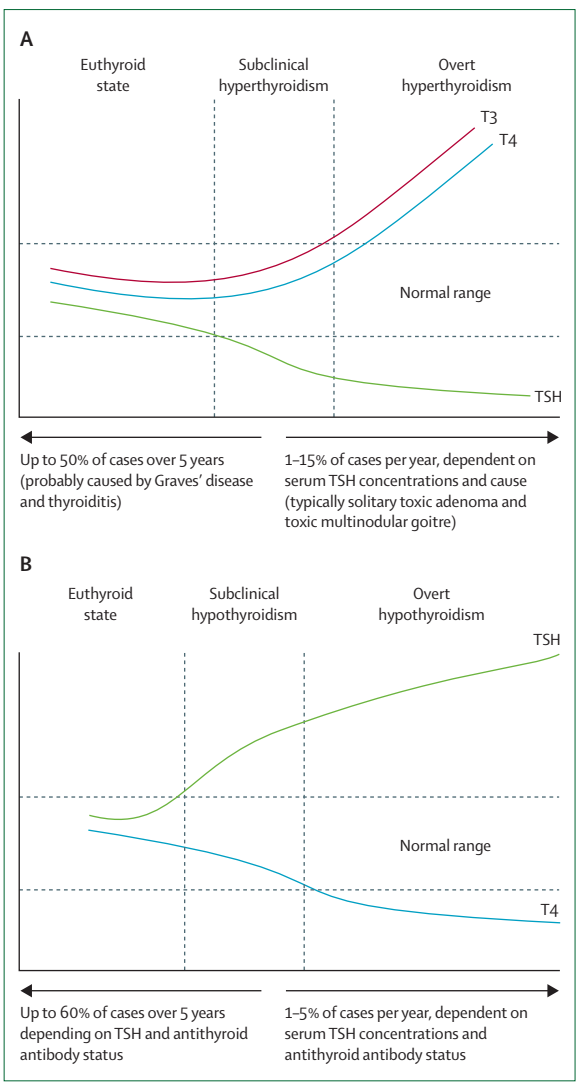

Figure 1: **Development and progression or regression of subclinical hyperthyroidism (A) and subclinical hypothyroidism (B)**
Both conditions can progress to overt disease or regress to an euthyroid state. T3=tri-iodothyronine. T4=thyroxine.

***Panel 1:* Classification of subclinical hyperthyroidism and other low serum TSH states**

Causes of persistent subclinical hyperthyroidism

Exogenous

- Iatrogenic (intentional or unintentional)

Endogenous

- Toxic multinodular goitre
- Solitary toxic nodule (solitary autonomous nodule)
- Graves' disease

Causes of transient subclinical hyperthyroidism

- Treatment of overt hyperthyroidism with antithyroid drugs or radioiodine
- Evolution of various forms of thyroiditis, including subacute thyroiditis (also called viral or DeQuervain's), silent thyroiditis (also called painless thyroiditis; typically develops in the postpartum period), and occasionally type 2 amiodarone-induced thyrotoxicosis (amiodarone-induced thyroiditis)

Causes of low serum TSH concentrations that are not subclinical hyperthyroidism*

- Low serum TSH at end of the first trimester of pregnancy[25]
- Low serum TSH seen in severe non-thyroidal illness and with treatment with high-dose glucocorticoids or dopamine
- Low serum TSH seen in some elderly individuals without apparent thyroid disease[15]
- Low serum TSH seen in some black individuals as a consequence of racial differences in the distribution of TSH concentrations in the general population[9]
- Low serum TSH seen in some smokers[16]
- Serum TSH below the reference range but at a normal concentration for that individual because the reference range only encompasses 95·0–97·5% of the general population

TSH=thyroid-stimulating hormone. *TSH usually >0·1 mU/L.

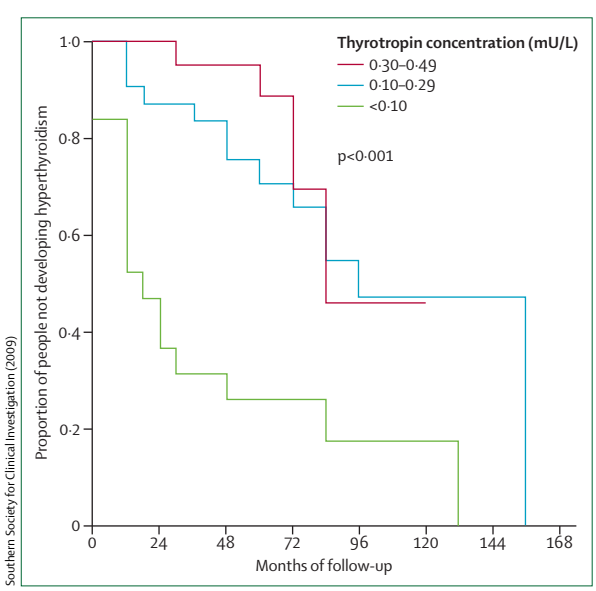

Figure 2: **Kaplan-Meier curves for time of follow-up without development of overt hyperthyroidism in patients with subclinical hyperthyroidism according to TSH concentrations**
Adapted from Díez and Iglesias,[13] by permission.

serum TSH and occasionally high free T4 concentrations occur at the end of the first trimester of pregnancy because of thyroidal stimulation by placental human chorionic gonadotropin, which has structural homology with TSH. Serum TSH will be less than 0·2 mU/L in up to 18% of pregnant women, most of whom will have normal free T4 concentrations.[25] Subclinical hyperthyroidism should also be differentiated from changes in thyroid function that are often seen in severely ill patients in hospital. In this euthyroid sick syndrome, the serum free T4 and T3 concentrations are typically low and TSH might also be subnormal. Thus, this laboratory scenario mimics central hypothyroidism, rather than subclinical hyperthyroidism.

Cardiovascular system

T3 has major effects on cardiac pacemaker function and vascular smooth muscle through non-genomic and genomic actions, and on myocardial contractility through effects on myocardial structural and regulatory gene transcription.[26,27] The resulting chronotropic, inotropic, and lusitropic (ie, diastolic relaxation) effects of excess thyroid hormone on the heart in overt hyperthyroidism are present to a lesser extent in subclinical hyperthyroidism, and thus might lead to increased cardiovascular morbidity and mortality. Patients with subclinical disease have a higher mean 24-h heart rate than do controls in a euthyroid state,[28,29] and have an increased frequency of premature atrial[28,29] and ventricular beats.[29] Findings of two small studies have shown an increased left ventricular mass[28,29] in patients with subclinical hyperthyroidism, but this observation has not been confirmed in large population-based studies.[30,31] Studies examining systolic and diastolic function with various non-invasive techniques have also yielded mixed results: systolic function has been reported to be normal in most,[29,32,33] but not all,[28] studies. Some investigators report impairment of diastolic function,[28,29] and others have seen no significant change.[32,34] Differences in age, degree of TSH suppression, duration, and cause of hyperthyroidism might explain these conflicting results.

Subclinical hyperthyroidism might be associated with changes in coagulation indicators.[35,36] Whether these changes are clinically relevant is not certain, but case reports describing thrombosis in patients with overt hyperthyroidism suggest the need for further research.[37] With respect to additional atherosclerotic risk factors, findings of a population-based study showed that patients with subclinical hyperthyroidism had increased carotid intima-media thickness compared with individuals in a euthyroid state or, surprisingly, those with mild hypothyroidism.[38] Patients with subclinical hyperthyroidism also had an increased frequency of carotid artery plaques and stroke.[39] Increased carotid intima-media thickness is associated with an increase in atherosclerotic cardiovascular events[40] and, thus, might be related to increased cardiovascular morbidity and mortality in subclinical hyperthyroidism, especially in elderly patients or in those with underlying cardiac disease.

Atrial fibrillation

The frequency of atrial fibrillation is increased in patients with subclinical hyperthyroidism. In a retrospective cross-sectional study of more than 23 000 people aged 65–70 years who were in hospital, most of whom had underlying cardiovascular disease, Auer and colleagues[41] reported a similar frequency of atrial fibrillation in subclinical hyperthyroidism (13%) and overt hyperthyroidism (14%), compared with 2% in controls in a euthyroid state. Findings of a subsequent population-based study of 5860 people aged 65 years or older showed atrial fibrillation to be present in 9·5% of people with subclinical hyperthyroidism versus 4·7% of controls,[42] with similar prevalence in people with serum TSH of less than 0·1 mU/L and in those with minimally suppressed serum TSH (0·1–0·4 mU/L).

A similar association between atrial fibrillation and subclinical hyperthyroidism was noted in two prospective studies of people older than 60 years.[11,43] In the more recent report,[11] risk of atrial fibrillation almost doubled across a 13-year follow-up in individuals with subclinical hyperthyroidism who were aged 65 years or older, and the risks were similar whether the serum TSH was less than 0·1 mU/L or 0·1–0·44 mU/L.

Cardiovascular and all-cause mortality

Increases in cardiovascular or all-cause mortality in subclinical hyperthyroidism have been recorded in some studies,[44–46] but not in other similarly designed prospective cohort studies.[11,47–49] Findings of three meta-analyses showed no increase in circulatory or all-cause mortality in patients with subclinical disease.[50–52] By contrast, in a fourth meta-analysis, which included several studies that had been excluded in the previous meta-analyses, risk of all-cause mortality was increased in subclinical hyperthyroidism (hazard ratio [HR] 1·41, 95% CI 1·12–1·79).[53] From a mathematical simulation of hypothetical cohorts of patients, the risk of death increased progressively over time, with the highest risk in the elderly (figure 3), and was higher in men than in women.[53]

The skeleton

Thyroid hormone stimulates bone resorption by a direct effect on osteoclast function. Overt hyperthyroidism is associated with increased bone turnover and an increased risk of osteoporosis and fracture.[54] In most studies of endogenous subclinical hyperthyroidism and bone health, bone mineral density is decreased in postmenopausal women,[55–56] especially in cortical bone-rich sites such as the distal radius, but we identified little evidence of an effect on bone in men or premenopausal women,[57] with the exception of one study.[58]

Whether postmenopausal women with subclinical hyperthyroidism have an increased risk of fracture is uncertain: in a cohort of 686 women aged 65 years or older who were followed up for about 4 years, occurrence of vertebral fractures was four-times higher and occurrence of hip fractures was three-times higher in women with baseline serum TSH of less than 0·1 mU/L than in those with normal TSH concentrations.[59] In another prospective study of individuals older than 65 years who were followed up for a median of 13 years (IQR 7·8–14·5), the incidence of hip fracture was higher in men, but not in women, with subclinical hyperthyroidism than in controls in a euthyroid state (HR 4·91, 95% CI 1·13–21·27).[60]

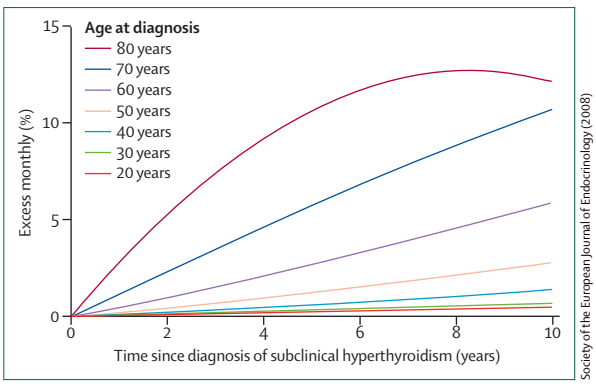

Figure 3: **Excess all-cause mortality in men with subclinical hyperthyroidism according to a meta-analysis of aggregated data from cohort studies and life-tables**
Reproduced from Haentjens and colleagues,[53] by permission.

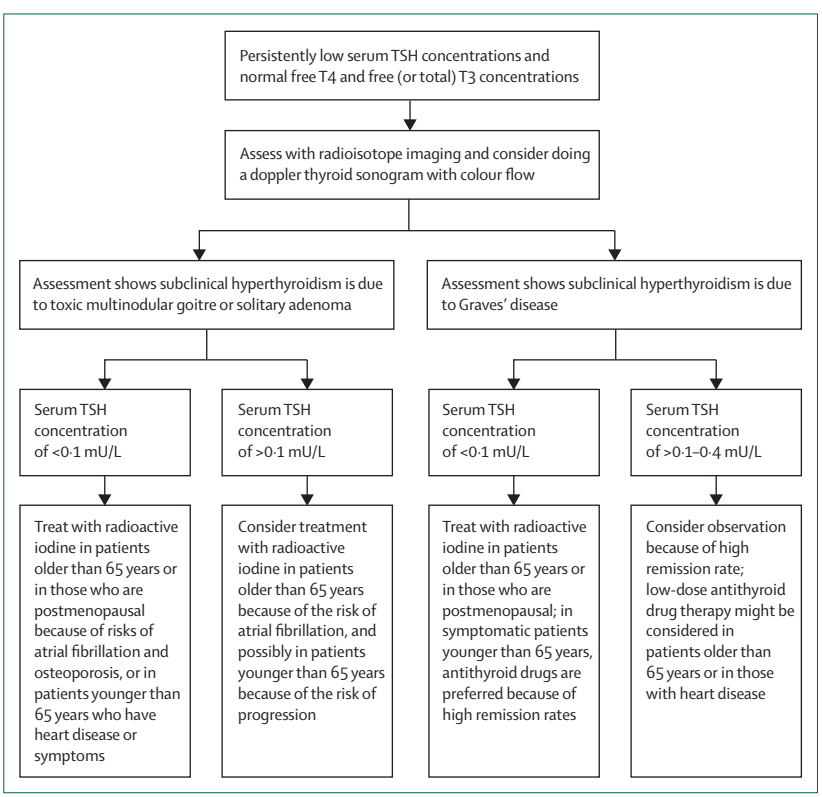

Figure 4: **Algorithm for assessment and treatment of subclinical hyperthyroidism**
This figure shows the algorithm outlined in panel 2. TSH=thyroid-stimulating hormone. T4=thyroxine. T3=tri-iodothyronine.

Panel 2: **Scheme for assessment and treatment of subclinical hyperthyroidism**

Laboratory testing

Thyroid imaging is reasonable in cases with persistently low serum TSH concentrations, especially those with less than 0·1 mU/L (figure 4). Radionuclide thyroid scanning with either ^{123}I or ^{99m}Tc can assess for areas of autonomy. Colour-flow doppler sonography can reveal nodules that could be autonomous, the presence of a multinodular goitre, or a pattern suggestive of autoimmune disease. Measurements of anti-thyroid antibodies (especially antithyroid peroxidase antibodies) and anti-TSH receptor antibodies could also be done in patients with suspected Graves' disease. Fine-needle biopsy should be considered in patients with suspicious nodules by sonography. In postmenopausal women, assessment of bone mineral density should be considered, because the presence of osteoporosis would favour treatment. Anticoagulation should be considered if atrial fibrillation is present.

Treatment of patients with serum TSH concentrations of less than 0·1 mU/L

In patients older than 65 years who have low serum TSH concentrations that are secondary to toxic multinodular goitre or a solitary autonomous solitary nodule, radioactive iodine is a definitive and preferred form of treatment because spontaneous remission is unlikely to occur. In patients with Graves' disease, treatment with either antithyroid drugs or radioiodine is appropriate. If specific treatment is not offered, reasonable alternatives would be provision of a β-adrenergic-blocking drug in patients at risk for atrial fibrillation, and calcium supplementation and treatment with a bisphosphonate in postmenopausal women with osteoporosis. American Thyroid Association guidelines[77] also recommend consideration of treatment in symptomatic individuals younger than 65 years because of the results of an uncontrolled study.[29] In asymptomatic patients younger than 65 years who do not have cardiac risk factors or in premenopausal women, no evidence is available for benefit of treatment. However, patients with toxic multinodular goitre or solitary toxic adenomas, in contrast to those with Graves' disease, have a risk of progression to overt hyperthyroidism, so that treatment with radioactive iodine could be considered.[10] Surgery would be an option in patients with subclinical hyperthyroidism and compressive symptoms from a large goitre. Untreated patients need follow-up of thyroid function every 6–12 months. Also, patients with underlying multinodular goitre and subclinical hyperthyroidism are at risk for development of iodine-induced thyrotoxicosis if they are exposed to iodine-containing drugs or contrast media, so such exposure should be avoided if possible.

Treatment of patients with serum TSH concentrations of 0·1–0·4 mU/L

Patients whose serum TSH concentrations are only minimally suppressed might not need treatment. Some patients regain normal thyroid function whereas others progress. Evidence for benefit is lacking, but in view of the increased risk of atrial fibrillation in people older than 65 years who have mildly suppressed serum TSH concentrations,[11] treatment might be reasonable in this age-group, especially if clear-cut abnormalities can be shown on thyroid imaging. In patients older than 65 years, a 12-month course of treatment should be considered in patients with Graves' disease (antithyroid drugs) or radioactive iodine therapy in those with nodular thyroid disease.

TSH=thyroid-stimulating hormone.

Zaidi and colleagues[61] have suggested that increased bone turnover and bone loss in hyperthyroidism could be related in part to TSH deficiency rather than to excess of thyroid hormone. This intriguing possibility, although controversial,[62] is supported by the presence of TSH receptors in bone and by short-term studies in animals and human beings,[63] but requires confirmation.

Symptoms, quality of life, and cognitive function

Young and middle aged patients with subclinical hyperthyroidism can have palpitations, heat intolerance, and anxiety,[28,29] with a reduction in quality-of-life scores.[28] In several population-based cohorts, however, no symptoms or changes in mood or cognitive function could be discerned.[44,64,65] Subclinical hyperthyroidism in elderly people has been associated with dementia in two prospective community-based samples[66,67] and two case-control studies,[68,69] but not in a large cross sectional study[70] or another prospective study.[71]

Treatment

Although subclinical hyperthyroidism is a common and important problem, few prospective randomised controlled studies have been done to assess treatments. Findings of small uncontrolled studies have shown improvements according to several indicators: reduced mean heart rate, cardiac output, and systemic vascular resistance;[72] decreased left ventricular mass index and frequency of atrial and ventricular premature beats;[29] and decreased 24-h mean heart rate and ventricular premature beats, but not atrial premature beats.[73] In patients with subclinical hyperthyroidism and atrial fibrillation, some evidence supports spontaneous conversion to normal sinus rhythm after treatment.[41]

In two prospective studies in postmenopausal women with subclinical hyperthyroidism, treatment led to stabilisation or mild improvement in bone mineral density, whereas untreated patients had a progressive decline in bone mineral density.[56,74] Findings of a small randomised study in women with a mean age of 58 years showed an improvement in bone mineral density, assessed by heel ultrasonometry (the stiffness index),[73] after 1 year of antithyroid drug treatment and normalisation of thyroid function. No prospective data are available for fracture risk in treated versus untreated women. 6 months of antithyroid drug treatment had no obvious clinical benefit to skeletal health in premenopausal women with subclinical hyperthyroidism, according to the findings of a small prospective randomised study.[75] However, after restoration of the euthyroid state by treatment, middle-aged patients with subclinical hyperthyroidism had an increase in thigh muscle strength in a non-randomised study.[76] In an uncontrolled study, treatment of subclinical hyperthyroidism led to a decrease in hyperthyroid symptoms according to the Wayne index, a validated hyperthyroid clinical score.[29] Figure 4 and panel 2 show an algorithm for clinical management of patients with subclinical hyperthyroidism.

Subclinical hypothyroidism

Disease forms

Most experts agree that subclinical hypothyroidism represents early, mild thyroid failure. Dependent on the size of the increase in serum TSH, subclinical hypothyroidism can be mild (serum TSH concentrations

of 4·5–9 mU/L) or severe (TSH ≥10 mU/L).[78] At least 75% of patients with subclinical disease have mild thyroid dysfunction (TSH ≤10 mU/L).[5] The definition and the clinical significance of subclinical hypothyroidism are confounded by controversies over the correct upper limit of the reference range for serum TSH.[78,79] Some investigators regard the hormonal pattern associated with mild subclinical disease as a compensated state in which high serum TSH serves to maintain normal circulating thyroid hormone concentrations,[78] but most investigators judge raised TSH concentrations to be a marker of true, albeit mild, thyroid hormone deficiency.[80]

Cause

Subclinical hypothyroidism has various causes (panel 3). In about 60–80% of cases, the disorder is associated with antithyroid peroxidase antibodies, a marker of chronic lymphocytic (Hashimoto's) thyroiditis. Hashimoto's thyroiditis is more common in girls and women, and the overall incidence increases with age in both sexes. Patients with treated overt thyroid failure often have subclinical hypothyroidism[5,6,9] because of inadequate thyroid hormone supplementation, poor adherence, drug interactions, or inadequate monitoring of treatment.

Epidemiology

Subclinical hypothyroidism is more common in iodine-sufficient countries, and iodine supplementation might increase the incidence.[81] Subclinical hypothyroidism occurs in 4–20% of the adult population. This wide range is a result of differences in age, sex, body-mass index, race, dietary iodine intake, and the cutoff concentrations of serum TSH that are used to define the condition. The prevalence of subclinical hypothyroidism in the US population was 4·3% in NHANES III,[9] and 9·5% in the Colorado Study of more than 25 000 people attending statewide health fairs.[5] The prevalence of raised serum TSH concentrations is higher in white than in black populations, supporting a genetic effect on TSH secretion.[9]

Diagnosis

Predisposition to autoimmune thyroiditis might be increased by familial and genetic risk factors, such as family history of autoimmune thyroid disease, endocrine or systemic autoimmune disorders, or genetic disorders (eg, Down's syndrome and Turner's syndrome). Ultrasound can reveal the typical pattern of hypoechogenicity, heterogeneity, and increased blood flow seen in autoimmune thyroiditis.[82] High antithyroid autoantibody titres are associated with persistently raised serum TSH concentrations.[83]

Differential diagnosis

Subclinical hypothyroidism should be distinguished from other causes of physiological, artifactual, or transiently increased serum TSH (panel 3). Serum TSH concentrations should be reassessed after 3–6 months to rule out laboratory error or a transient increase, for example, by drugs that interfere with thyroid function, thyroiditis, and possible toxic injury to the thyroid gland (panel 3).

Serum TSH concentrations might be artifactually raised from heterophilic antibodies against mouse proteins in some immunoassays (panel 3). In healthy individuals, serum TSH concentrations are higher in

***Panel 3:* Causes of subclinical hypothyroidism and differentiation from other causes of increases in serum TSH concentrations**

Causes of persistent subclinical hypothyroidism

- Chronic autoimmune thyroiditis
- Partial thyroidectomy
- Radioactive iodine therapy for treatment of hyperthyroidism
- External radiotherapy of the head and neck in patients with Hodgkin's lymphoma, leukaemia, aplastic anaemia, brain tumours, or bone-marrow transplantation
- Infiltrative disorders of the thyroid gland (eg, amyloidosis, sarcoidosis, haemochromatosis, or Riedel's thyroiditis)
- Persistent TSH increase after an episode of subacute thyroiditis, post-partum thyroiditis, or painless thyroiditis
- Drugs impairing thyroid function in patients with autoimmune thyroiditis (iodine and iodine-containing drugs, such as amiodarone and radiographic contrast agents, lithium carbonate, cytokines [especially interferon alfa], or kinase inhibitors)
- Inadequate replacement therapy for overt hypothyroidism because of one of the following reasons: inadequate dose; increased need for levothyroxine (increased body weight and pregnancy); non-compliance; drug interactions (ferrous sulfate, calcium carbonate, colestyramine, sucralphate, orlistat, possibly dietary soy and fibre, proton-pump inhibitors, aluminum hydroxide, ion exchange resins, raloxifene, or oestrogens); increased T4 clearance (phenytoin, carbamazepine, or phenobarbital); malabsorption (eg, *Helicobacter pylori* infection, coeliac disease, or atrophic gastritis); or toxic substances, industrial, and environmental agents (eg, polychlorinated biphenyls)
- Thyroid dysgenesis
- Iodine deficiency

Causes of physiological or transient increases in serum TSH concentrations

- Diurnal variation with a nocturnal surge and highest values early in the morning
- Recovery phase from non-thyroidal illness
- After withdrawal of thyroid hormone therapy in patients in a euthyroid state
- Transient subclinical hypothyroidism after subacute, painless, or post-partum thyroiditis

Causes of increased serum TSH concentrations that are not subclinical hypothyroidism

- Laboratory analytical problem (assay variability, abnormal TSH isoforms, or heterophilic antibodies)
- Elderly patients with small increases in serum TSH concentrations
- Obesity
- TSH-secreting pituitary adenoma
- Isolated pituitary resistance to thyroid hormone
- TSH with reduced biological activity
- Impaired renal function
- Untreated adrenal insufficiency
- Serum TSH concentration outside of the reference range but normal for that individual because the reference range only encompasses 95–97·5% of normal individuals

TSH=thyroid-stimulating hormone. T4=thyroxine.

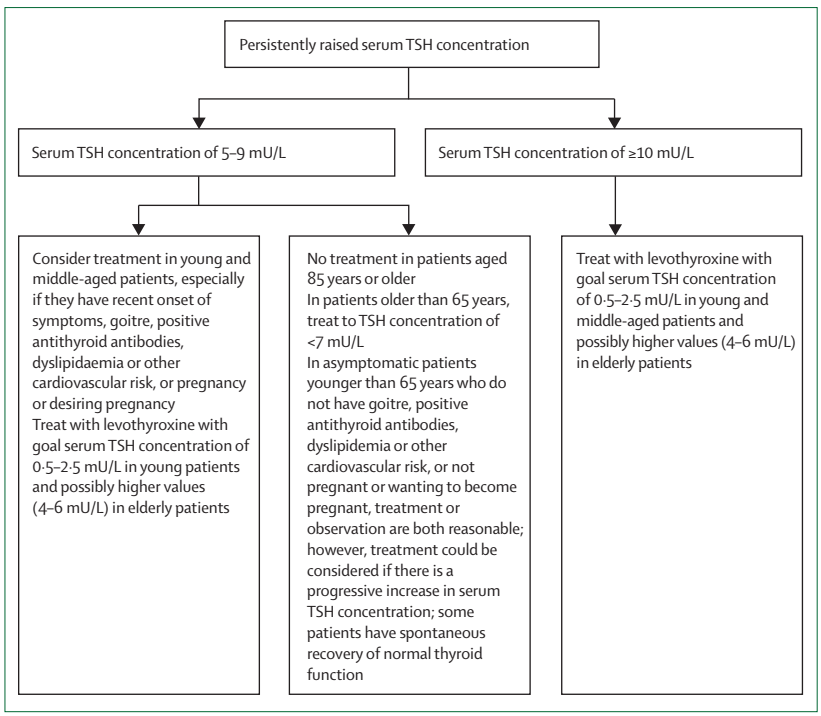

Figure 5: **Algorithm for treatment of subclinical hypothyroidism**
This figure shows the algorithm outlined in panel 4. TSH=thyroid-stimulating hormone. T4=thyroxine.

elderly than in young people[84] because of a shift in the TSH distribution with age.[85] However, this increase probably does not indicate thyroid hormone deficiency because it has been recorded in individuals without circulating antithyroid antibodies, goitre, or a family history of thyroid disease.[85] Rarely, a laboratory pattern indistinguishable from subclinical hypothyroidism is seen in patients with TSH-receptor mutations causing mild TSH resistance, which can affect up to 0·6% of white people.[86] Clues to the existence of this disorder are a family history of raised serum TSH concentrations and an absence of thyroid autoimmunity.

Serum TSH concentrations are raised in overweight and obese individuals, which might falsely suggest subclinical hypothyroidism.[87] In fact, the mild increase in serum TSH concentrations in obese people is usually associated with serum concentrations of free T3 at the upper boundary of the normal range, which might be caused by increased de-iodinase activity as a compensatory mechanism for fat accumulation to raise energy expenditure. This altered thyroid hormone pattern is reversible with weight loss.[87]

Progression to overt hypothyroidism

Subclinical hypothyroidism is usually progressive, although it is reversible in more cases than previously thought, especially when serum TSH concentrations are 10 mU/L or lower.[88] Serum TSH of more than 10 mU/L, female sex, and the presence of antithyroid peroxidase antibodies are associated with an increased risk of progression to overt hypothyroidism. In patients with antithyroid peroxidase antibodies, a high iodine intake is a further risk factor for development of overt hypothyroidism.[89] Serum TSH of more than 2·5 mU/L and presence of thyroid autoantibodies were predictors of long-term risk of hypothyroidism in three longitudinal studies.[89–91] The annual rate of progression to overt disease was about 4% in women with raised serum TSH and positive antithyroid antibodies, 2–4% in those with only raised serum TSH concentrations, and 1–3% in those with only antithyroid antibodies present. However, in another population of 422 242 patients, progression from slightly increased serum TSH (>5·5 to ≤10 mU/L) to high TSH (>10 mU/L occurred in only 2·9% of cases during 5 years of follow-up.[18] Serum TSH values tend to return to normal more frequently in people with concentrations of 4–6 mU/L, whereas TSH values of more than 10–15 mU/L are associated with a reduced rate of normalisation of thyroid function.[88]

Symptoms

The symptoms of hypothyroidism are neither sensitive nor specific. Indeed, patients in a euthyroid state are difficult to distinguish from those with subclinical hypothyroidism because symptoms are affected by disease severity, disease duration, and individual sensitivity to thyroid hormone deficiency. Patients who report many or newly developed symptoms are most likely to have thyroid hormone deficiency.[5] Quality of life, anxiety, symptoms of depression, cognitive function, and memory can be altered in patients with subclinical hypothyroidism, although contrasting findings have been reported.[92–99] Subclinical hypothyroidism seems to be less symptomatic in elderly people.[44,100–102] For example, in two large cross-sectional community-based studies, subclinical hypothyroidism was not associated with cognitive dysfunction, anxiety, or depression in patients aged 65 years or older.[49,64] In another community-based study of people aged 70–79 years, subclinical hypothyroidism was associated with increased walking speed and retention of physical function across a 2-year follow-up period compared with those with normal thyroid function.[101]

Cardiovascular risk

Patients with subclinical hypothyroidism can have depressed systolic function at rest, and left ventricular diastolic dysfunction at rest and during exercise.[102] Symptomatic patients might complain of reduced exercise tolerance during effort, and the slowed rate of left ventricular relaxation might critically impair ventricular filling during exercise, leading to left ventricular systolic dysfunction.[103] Vascular function can also be impaired by thyroid hormone deficiency.[104,105] Subclinical hypothyroidism can impair relaxation of vascular smooth muscle cells, inducing increases in

systemic vascular resistance and arterial stiffness,[104] and changes in endothelial function by reduction of nitric oxide availability.[98,105] However, the clinical significance of these findings is unknown.

The presence of several important cardiovascular risk factors in patients with subclinical hypothyroidism could affect treatment decisions. These factors include diastolic hypertension,[106,107] hypercholesterolaemia,[5,108] insulin resistance,[109] weight gain,[110] and isolated diastolic dysfunction.[104] In a reanalysis of data from the Whickham Survey cohort, systolic and diastolic blood pressures and total cholesterol concentrations were higher in patients with subclinical hypothyroidism than in controls in a euthyroid state.[111] However, in the EPIC-Norfolk study, although subclinical hypothyroidism was, perhaps paradoxically, associated with a worse cardiovascular risk profile than in controls in a euthyroid state, coronary heart disease and all-cause mortality did not increase across 10·6 years of follow-up.[112]

Hypothyroidism has been associated with dyslipidaemia, especially increased total and LDL cholesterol.[113] However, although the relation between overt hypothyroidism and serum lipids is well documented, this relation is controversial in patients with subclinical disease.[108] Overt thyroid hormone deficiency induces an increase in total cholesterol and in LDL cholesterol,[113] and the lipid pattern might also be altered in subclinical hypothyroidism, especially in patients with serum TSH of more than 10 mU/L,[95,108] in smokers,[114] and in insulin-resistant patients.[115] The associations of subclinical hypothyroidism with non-traditional cardiovascular risk factors, such as homocysteine, high-sensitive C-reactive protein, fibrinogen, factor VIII, von Willebrand factor, and lipoprotein(a), are largely not signficant.[7]

Subclinical hypothyroidism has been associated with an increased risk of cardiovascular disease and mortality in some prospective population-based cohort studies.[111,116,117] By contrast, the incidence of coronary heart disease and mortality due to coronary heart disease were not increased in other prospective population-based studies.[11,46,112,118] In a meta-analysis of individual participant data from 11 prospective cohort studies, the risk of coronary heart disease increased with the severity of thyroid hormone deficiency.[119] By contrast with previous data suggesting that the risk of coronary heart disease decreased with patient age,[7] findings of this meta-analysis showed no interaction between mortality due to coronary heart disease and age.

Risk of heart failure

Two studies have assessed the relation between subclinical hypothyroidism and heart failure in elderly patients older than 65 years[120] or 70 years.[118] In one study, the relative risk of incident heart failure was 2·6 (95% CI 1·19–5·60) for patients with TSH of 7·0–9·9 mU/L and 3·26 (1·37–7·77) for those with serum TSH of 10 mU/L or greater.[118] In the other study, an increased incidence of heart failure was only recorded in patients with a TSH concentration of more than 10 mU/L.[120]

Panel 4: **Scheme for treatment of subclinical hypothyroidism**

Patients with serum TSH concentrations of 3–4·5 mU/L

Patients with serum TSH concentrations in this range can have increased rates of progression to overt hypothyroidism, therefore they should be monitored with periodic thyroid function tests, especially if they have positive antithyroid peroxidase antibodies. During pregnancy, serum TSH concentrations of more than 2·5 mU/L during the first trimester and of 3·1–3·5 mU/L during the second trimester are probably indicative of mild hypothyroidism. Pregnant women should be treated if they have TSH concentrations at the upper limit of the normal range for women who are not pregnant.[132,133] Women in a euthyroid state who have autoimmune thyroiditis in early gestation should be monitored during pregnancy for raised serum TSH concentrations during pregnancy.[132,133] Alternatively, such women could be treated with thyroid hormone, because findings of a prospective randomised trial showed a decrease in miscarriage rates with treatment.[134]

Patients with mild subclinical hypothyroidism, with serum TSH concentrations of 5–9 mU/L

Subclinical hypothyroidism might be associated with greater cardiovascular risk in young and middle-aged people than in people older than 65 years,[7] and therefore treatment is probably most justifiable in this age-group (figure 5). Furthermore, patients aged 61–80 years might not benefit because small increases in serum TSH (eg, TSH concentrations of 5–8 mU/L) are not indicative of true thyroid hormone deficiency in many cases.[84] Last, raised serum TSH concentrations might be associated with decreased mortality in people older than 85 years.[44] Patients with new onset of symptoms,[5] depression, goitre, positive antithyroid antibody tests, or cardiovascular risk factors (eg, hypertension, hypercholesterolaemia, insulin resistance or diabetes, or isolated diastolic dysfunction) might also benefit from treatment. If levothyroxine replacement has a beneficial effect, treatment should be continued and serum TSH concentrations should be assessed every 6–12 months to ensure that they remain within the normal range. Patients can progress to overt hypothyroidism, therefore increases in levothyroxine might be needed during follow-up. In the absence of clear-cut beneficial effects, replacement therapy should be stopped, and serum TSH concentrations should be assessed at yearly intervals. Available evidence[44,84] suggests that the benefit of treatment might be reduced in patients older than 65 years with serum TSH concentrations of 4·5–10 mU/L; if levothyroxine treatment is started, low doses (25–50 μg/day) should be used in patients with known coronary artery disease. Treatment of mild subclinical hypothyroidism is not recommended in elderly (older than 75 years) and very elderly (older than 80 years) patients because, aside from an increased risk of congestive heart failure in patients with serum TSH concentrations of more than 7–10 mU/L, there is no evidence that these patients are symptomatic, and levothyroxine treatment does not improve cognitive function or quality of life.

Patients with subclinical hypothyroidism with serum TSH concentrations of 10 mU/L or higher

Patients with high TSH concentrations have a significantly increased risk of progression to overt hypothyroidism, might be more frequently symptomatic, and might have an increased likelihood of cardiovascular disease. Treatment with levothyroxine is recommended in these patients. Replacement therapy should be individualised in elderly and very elderly patients with serum TSH concentrations of more than 10 mU/L. Low doses of levothyroxine are often adequate to normalise serum TSH concentrations in elderly patients. The target TSH serum concentration might be higher in individuals older than 70 years than in younger patients, to mimic physiological values (eg, 4–7 mU/L). Over-treatment with levothyroxine should be avoided because of the adverse cardiovascular and skeletal consequences of iatrogenic hyperthyroidism in elderly people.[8]

TSH=thyroid-stimulating hormone.

	Screening recommendations
ATA[135]	Women and men older than 35 years should be screened every 5 years
ATA[133]	Insufficient evidence to recommend for or against universal TSH screening in pregnant women
College of American Pathologists[136]	Women aged 50 years or older should be screened if they seek medical care; all geriatric patients should be screened on admission to the hospital and at least every 5 years
Association of Clinical Biochemistry, British Thyroid Association, and British Thyroid Foundation[137]	Screening for thyroid dysfunction in a healthy adult population is not warranted; case-finding in women at the menopause or in those with non-specific symptoms might be justified in view of the high prevalence of mild thyroid failure
American Academy of Family Physicians[138]	Insufficient evidence to recommend for or against routine screening for thyroid disease in adults
American College of Obstetrics and Gynecology[139]	Women in high-risk groups (those with autoimmune disease or a strong family history of thyroid disease) should be screened from age of 19 years onwards
American College of Physicians[140]	Women older than 50 years with an incidental finding suggestive of symptomatic thyroid disease should be screened
US Preventive Services Task Force[141]	Insufficient evidence to recommend for or against screening
US Institute of Medicine[142]	Screening is not justified in populations older than 65 years
Royal College of Physicians[143]	Screening of the healthy adult population is unjustified
ATA, AACE, The Endocrine Society consensus statement[78]	Population screening is unjustified; case-finding is recommended
The Endocrine Society[132]	Routine screening of pregnant women is not justified

ATA=American Thyroid Association. AACE=American Association of Clinical Endocrinologists.

Table: **Recommendations for screening adults for mild thyroid failure by professional societies and expert panels**

Women of reproductive age and during pregnancy

The prevalence of subclinical hypothyroidism in women during reproductive age is 0·5–5%, depending on the criteria used to assess TSH concentration.[121] Maternal subclinical hypothyroidism can lead to serious obstetric complications, including an increased risk of miscarriage,[122] placental abruption, and preterm delivery,[123] albeit at a lower frequency than is recorded in pregnant women with untreated overt hypothyroidism. Furthermore, gestational hypertension and low birthweight has been reported in 15% of pregnant women with subclinical hypothyroidism.[124] Thyroid hormone deficiency might induce preterm delivery[123,125] and is associated with an increased risk of fetal death in some,[122] but not all, studies.[123] In a study of serum TSH concentrations during pregnancy, more neonates born to mothers with subclinical hypothyroidism were admitted to the intensive care unit than were those born to women in a euthyroid state; this difference was due to an increased frequency of low birthweight, fetal distress, and neonatal respiratory distress.[126]

Thyroid hormone is essential for fetal brain development and maturation, and maternal transfer of thyroid hormone is essential, especially during the first trimester of pregnancy, because the fetal thyroid gland does not produce thyroid hormone until about 13 weeks of gestation. Impaired mental development has been reported in children born to women who were inadequately treated for subclinical hypothyroidism , but not in children born to women who were adequately treated.[127] What is unknown is whether the consequences of undiagnosed or untreated subclinical hypothyroidism on the developing brain are due to thyroid hormone deficiency per se or to the obstetric consequences of untreated subclinical disease.

Effects of replacement therapy

Various placebo-controlled studies have assessed the effects of levothyroxine replacement therapy on symptoms and signs in patients with subclinical hypothyroidism.[92–98] Comparison of these studies is difficult because enrolled patients differed in terms of the cause of disease, age, and degree of thyroid hormone deficiency, and the studies varied in terms of symptom scores, duration of replacement therapy, and levothyroxine dose. Furthermore, euthyroidism was not reached in all studies, especially when a fixed levothyroxine dose was used. Generally, however, levothyroxine treatment does not improve mood, cognition, or symptoms in patients with subclinical hypothyroidism unless the serum TSH concentration is more than 10 mU/L.[95]

The negative effects of subclinical hypothyroidism on cardiovascular function might be improved or reversed by replacement doses of levothyroxine. Although only a few studies of the cardiovascular effects of levothyroxine are double blind and placebo controlled,[92,93,98,128–130] findings of all these trials concur that replacement therapy improves systolic and diastolic function, endothelial function,[97] and carotid intima-media thickness.[130] The effects of subclinical hypothyroidism on heart failure and mortality have been indirectly assessed in two studies. Patients with subclinical hypothyroidism who were treated with levothyroxine had significantly lower risk of heart failure events in the Cardiovascular Health Study,[120] and significantly lower all-cause mortality in the Whickham Survey,[111] than did untreated individuals.

Eight placebo-controlled randomised clinical trials have examined the effects of levothyroxine on serum lipids in subclinical hypothyroidism.[92–96,98,130,131] Levothyroxine did not reduce total cholesterol in four studies,[92–94,96] but exerted a beneficial effect in the other four studies.[95,98,130,131] In a meta-analysis of 13 studies of the effects of levothyroxine treatment on serum cholesterol concentrations in 200 patients with subclinical hypothyroidism, the effects of replacement therapy with levothyroxine were proportional to both the severity of hypothyroidism and the increase of lipids.[108] Serum total cholesterol was reduced by about 0·2 mmol/L (5%) and serum LDL cholesterol by about 0·3 mmol/L after levothyroxine treatment, whereas triglyceride and HDL cholesterol concentrations did not change. Changes in lipid concentrations were not significant in patients with baseline serum cholesterol concentrations of less than 6·2 mmol/L, when only high-quality studies were analysed, or in patients with de-novo

subclinical hypothyroidism, compared with those with subclinical disease because of inadequately treated overt hypothyroidism.

Miscarriage rates and premature deliveries are much lower in women with subclinical hypothyroidism who are adequately treated during pregnancy than in women who are inadequately treated.[121,132] Treatment of thyroid hormone deficiency is not associated with adverse perinatal outcomes.[133] Whether levothyroxine treatment improves the neurological development of offspring has not been established, but because of the potential benefits of subclinical hypothyroidism treatment in pregnancy, treatment is recommended in clinical practice guidelines.[132,133] Figure 5 and panel 4 show an algorithm for clinical management of patients with subclinical hypothyroidism.

Screening

Population screening for subclinical hypothyroidism is controversial because the benefits of treatment are unproven for most individuals who might be diagnosed through screening programmes.[7] The recommendations for screening differ substantially between professional societies and expert panels (table). Case finding in high-risk groups has been advocated, especially in pregnant women and women who want to become pregnant. In a study of case finding, up to 30% of pregnant women with subclinical hypothyroidism were not diagnosed,[144] but findings of a randomised trial in pregnant women showed that universal screening did not reduce the rate of adverse events compared with case finding.[146] In a preliminary placebo-controlled trial, however, only 1% of middle-aged and older individuals had improved quality of life from screening for subclinical hypothyroidism and subsequent levothyroxine treatment.[146]

Conclusions

Subclinical thyroid disease is a common clinical problem, and since most patients are asymptomatic, screening is the only way that most patients with the condition will be detected. Yet, experts do not agree about whether screening to diagnose the disease is worthwhile, because there are no large, population-based randomised controlled trials showing that intervention is beneficial to patients. The data are sufficient, however, to recommend treatment of individuals with subclinical hyperthyroidism who are older than 65 years of age with serum TSH concentrations less than 0·1 mU/L, and people with subclinical hypothyroidism who have serum TSH concentrations of 10 mU/L or more. Treatment can also be recommended in pregnant women with serum TSH concentrations that are above the reference range for pregnancy. For most patients who have more mildly low or high serum TSH concentrations in between the extremes (ie, 0·1–0·5 mU/L and 5·0–10·0 mU/L, respectively), no firm recommendations can be made, and the decision to treat or not to treat a patient will be based on various clinical factors. Until the results of large-scale randomised clinical trials are available, clinicians will need to rely on their own clinical judgment and well-meaning, but necessarily vague clinical practice guidelines and expert opinions.

Contributors

DSC and BB contributed equally to the search for published studies, data interpretation, and writing and revision of this Seminar.

Conflicts of interest

DSC and BB have been speakers at symposia organised by Merck Serono. BB is part of the Editorial Board of *European Journal of Endocrinology*, *Thyroid*, and *European Thyroid Journal*. DSC is a member is an editor for *UpToDate* and receives book royalties from Ballantine Books and Informa Healthcare.

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