EDITORIAL

Subclinical hypothyroidism
Giampaolo Papi, Ettore degli Uberti, Corrado Betterle, Cesare Carania, Elizabeth N. Pearce, Lewis E. Braverman and Elio Roti

Purpose of review
Mild or subclinical hypothyroidism is characterized by normal serum free thyroxine concentrations with elevated serum thyroid-stimulating hormone concentrations. Subclinical hypothyroidism is relatively prevalent in the general population, especially among women and the elderly. The main cause of subclinical hypothyroidism is autoimmune chronic thyroiditis. The present report reviews the most important and recent studies on subclinical hypothyroidism, and discusses the most controversial aspects of this topic.

Recent findings
Several studies have demonstrated that subclinical hypothyroidism may affect both diastolic and systolic cardiac function. It may also worsen many risk factors for cardiovascular disease, including hypertension, abnormal endothelial function, and elevated low-density lipoprotein cholesterol concentrations. Furthermore, a growing body of evidence suggests that subclinical hypothyroidism may cause symptoms or progress to symptomatic overt hypothyroidism.

Summary
Prompt treatment of subclinical hypothyroidism in pregnant women is mandatory to decrease risks for pregnancy complications and impaired cognitive development in offspring. Children with subclinical hypothyroidism should be treated to prevent growth retardation. Whether nonpregnant adult patients with subclinical hypothyroidism should be treated, and at what thyroid-stimulating hormone values, is debatable.

Keywords
diagnosis, etiology, mild hypothyroidism, subclinical hypothyroidism, therapy

Abbreviations
AACE American Association of Clinical Endocrinologists
ATA American Thyroid Association
HDL-C high-density lipoprotein-cholesterol
LDL-C low-density lipoprotein-cholesterol
SCH subclinical hypothyroidism
TPO-Ab thyroperoxidase antibody
TSH thyroid-stimulating hormone

Introduction
Patients with overt thyroid dysfunction should be treated [1,2]. However, whether and when treatment should be started in patients with subclinical hyperthyroidism or subclinical hypothyroidism (SCH) is still debatable [3–11]. Although the Endocrine Society, the American Association of Clinical Endocrinologists (AACE) and the American Thyroid Association (ATA) have stated their position about the appropriate management of subclinical thyroid disorders, the controversy still remains unresolved, especially related to SCH [12].

In the last few years, several groups have investigated whether SCH may be associated with symptoms, may represent a risk factor for cardiovascular disease, or may evolve to overt hypothyroidism. The role of L-thyroxine therapy in reducing or reversing the adverse effects of SCH has also been evaluated.

The present report reviews the most important and recent studies related to SCH and attempts to draw literature-based conclusions about the management of this condition.

Definition
A recent consensus committee defined SCH as a serum thyroid-stimulating hormone (TSH) concentration above the statistically defined upper limit of the reference range and the serum free thyroxine within the reference range [13].

The third National Health and Nutrition Examination Survey (NHANES III) [14] screened 13,344 disease-free, euthyroid subjects who were thyroid antibody negative. In this population, the median TSH concentration was 1.39 mIU/l, with the 95% TSH reference limits between
As serum TSH varies over time in healthy subjects, leading to occasional abnormal values [19–21], repeat serum TSH along with free thyroxine measurements within 3–4 months is required. If elevated serum TSH concentrations are confirmed, and free thyroxine values are within the normal range, the diagnosis of SCH is made, and transient forms of SCH are unlikely. Normal serum free thyroxine concentrations may also be found in patients with frankly elevated serum TSH concentrations. Before considering further causes of persistently elevated TSH values, the presence of heterophilic antibodies, which may cause falsely elevated serum TSH concentrations, must be excluded [22–24]. Klee and Hay [25] reported that only 23% of patients with serum TSH concentrations higher than 20 mIU/l had serum free thyroxine values lower than 0.6 ng/100 ml. Others [7,26] have postulated that 5% of the normal population with TSH values exceeding 2.5 mIU/l represent ‘euthyroid outliers’. Reducing the upper limit of normal from 5 to 2.5–3 mIU/l has extremely important practical consequences, with the prevalence of SCH increasing from 4.6 to 20% in the general population [27]. For some authors, SCH is a well characterized disease with a cohort of signs and symptoms and, therefore, should be treated [6]; for others, it represents just a laboratory abnormality [28] and may be considered a mere laboratory aberration [29]. Recent data reviewed below suggest that SCH should not be considered a mere laboratory abnormality [28] and may represent a well defined, often clinically relevant disease characterized by thyroid hormone production that is persistently insufficient to maintain euthyroidism.

**Etiology**

Table 1 summarizes the causes of SCH and distinguishes between progressive and potentially reversible or transient SCH.

SCH is most commonly caused (50–80% of cases) by chronic autoimmune thyroiditis, which is typically characterized by hypochoogenicy on ultrasound thyroid examination and by the presence of thyroid autoantibodies in the serum, most commonly against thyroperoxidase antibodies (TPO-Ab), less commonly thyroglobulin antibodies, and rarely TSH-receptor blocking antibodies [29]. Less frequently, SCH is due to other conditions. Inflammatory thyroiditis may lead to transient SCH following a short thyrotoxic phase and overt hypothyroidism may develop up to years later. Patients who have previously undergone partial thyroidectomy and those treated with 131I may develop SCH. Patients treated with external neck X-ray therapy, especially during infancy and adolescence, may also develop SCH years later, which can progress to overt disease. Finally, SCH is diagnosed in 17.6% of l-thyroxine-treated hypothyroid patients due to insufficient l-thyroxine administration [30].

**Epidemiology**

SCH prevalence ranges between 4 and 10% in the general population [14,30–33] and between 7 and 26% in the elderly [30,31,34–39]. The prospective Whickam survey reported a 7.5% prevalence of SCH in women, and 2.8% in men; in women aged >60 years it was 11.6% [40]. In the Colorado Thyroid Disease Prevalence Study, a cross-sectional study of 25,862 health-fair participants, SCH was defined as serum TSH concentrations >5 mU/ml with normal thyroid hormone values, and an overall prevalence of 9.5% was found, varying according to age and sex; 4% in 18–24-year-old subjects, and 16 and 22% in men and women over age 74 not taking l-thyroxine, respectively [30]. As autoimmune thyroiditis is a major cause of SCH, it is not surprising that other autoimmune diseases also occur in patients with SCH, including type 1 diabetes mellitus in adults and children [41,42], autoimmune adrenal insufficiency (Schmidt’s syndrome; also termed autoimmune polyendocrine syndrome type 2) [43], and celiac disease (autoimmune polyendocrine syndrome type 3B) in both children and adults [44,45]. Young patients with β-thalassemia are also at risk for developing SCH and iodine-induced hypothyroidism [46,47].

Women with postpartum lymphocytic thyroiditis may subsequently develop SCH and overt hypothyroidism following administration of excess iodine [48–51]. Similarly, patients with sporadic lymphocytic thyroiditis may experience transient SCH after a spontaneously resolving period of thyrotoxicosis. The presence of both thyroid-stimulating and TSH-binding inhibiting immunoglobulins has been etiologically related to the

**Table 1 Causes of subclinical hypothyroidism**

<table>
<thead>
<tr>
<th>Causes of probably progressive subclinical hypothyroidism</th>
<th>Causes of potentially reversible/transient subclinical hypothyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid dysgenesis</td>
<td>Subacute (De Quervain’s) thyroiditis</td>
</tr>
<tr>
<td>Partial thyroidectomy</td>
<td>Sporadic silent thyroiditis</td>
</tr>
<tr>
<td>Neck external beam radiotherapy</td>
<td>Postpartum thyroiditis</td>
</tr>
<tr>
<td>131I treatment of hyperthyroidism</td>
<td>Amiodarone-induced hypothyroidism</td>
</tr>
<tr>
<td>Chronic (Hashimoto’s) thyroiditis</td>
<td>Cytokine-induced hypothyroidism</td>
</tr>
<tr>
<td>Riedel’s thyroiditis</td>
<td>Lithium-induced hypothyroidialtism</td>
</tr>
<tr>
<td>Severe iodine deficiency</td>
<td>Antithyroid drugs (methimazole, propylthiouracil)</td>
</tr>
<tr>
<td></td>
<td>Addison’s disease</td>
</tr>
</tbody>
</table>

Causes of probably progressive subclinical hypothyroidism:
- Severe iodine deficiency
- Antithyroid drugs (methimazole, propylthiouracil)
- Addison’s disease

Causes of potentially reversible/transient subclinical hypothyroidism:
- Subacute (De Quervain’s) thyroiditis
- Sporadic silent thyroiditis
- Postpartum thyroiditis
- Amiodarone-induced hypothyroidism
- Cytokine-induced hypothyroidism
- Lithium-induced hypothyroidism
- Antithyroid drugs (methimazole, propylthiouracil)
- Addison’s disease

Causes of potentially reversible/transient subclinical hypothyroidism:
- Subacute (De Quervain’s) thyroiditis
- Sporadic silent thyroiditis
- Postpartum thyroiditis
- Amiodarone-induced hypothyroidism
- Cytokine-induced hypothyroidism
- Lithium-induced hypothyroidism
- Antithyroid drugs (methimazole, propylthiouracil)
- Addison’s disease

Causes of probably progressive subclinical hypothyroidism:
- Severe iodine deficiency
- Antithyroid drugs (methimazole, propylthiouracil)
- Addison’s disease
occurrence of either overt hypothyroidism or SCH in subjects with lymphocytic thyroiditis [52].

Approximately 2–5% of patients with SCH will progress to overt hypothyroidism annually [13]. The rate of progression is proportional to the baseline serum TSH concentration and is higher in patients with elevated thyroid autoantibodies [40]. Recently, Huber and coworkers [53] reported the results of a long-term prospective study (mean observation period of 9.2 years) performed to evaluate the spontaneous course of SCH, and the value of predictive factors in the development of overt hypothyroidism. SCH persisted in 57% of patients, in 34% overt hypothyroidism developed, whereas in 9% of subjects’ sera TSH concentrations reverted to normal. The higher the initial serum TSH concentrations, the greater the risk of progression to overt hypothyroidism. For those with baseline serum TSH concentrations >6 mIU/l, the cumulative incidence was 55.3%. The incidence of overt hypothyroidism significantly increased in patients with impaired thyroid reserve (32.6 compared with 38.1%) and positive microsomal antibodies (58.5 compared with 23.2%). Normalization of SCH has also been reported. In the absence of L-thyroxine therapy, all 40 patients in one study normalized their TSH values within a median of 18 months [54]. It should be emphasized that these ‘normalized’ TSH values were higher than 2.5 mIU/l.

The progression of SCH to overt hypothyroidism is also related to the degree of hypoechogenicity of the thyroid gland on ultrasound. Diffuse thyroid hypoechogenicity, consistent with a diagnosis of autoimmune thyroiditis, was found in 18.5% of 1184 subjects. The degree of hypoechogenicity correlated with the levels of circulating thyroid autoantibodies, and was predictive of the development of hypothyroidism in some patients [55].

**Somatic and neuropsychologic symptoms/signs**

Table 2 summarizes the main symptoms/signs of hypothyroidism reported in approximately 30% of patients with SCH [28,56–63].

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor memory</td>
<td>Constipation</td>
</tr>
<tr>
<td>Slow thinking</td>
<td>Hoarseness</td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>Generalized swelling</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Weight gain</td>
</tr>
<tr>
<td>Muscle cramps</td>
<td>Cognitive dysfunction</td>
</tr>
<tr>
<td>Cold intolerance</td>
<td>Lower amplitude of stapedial reflex</td>
</tr>
<tr>
<td>Depression</td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td></td>
</tr>
</tbody>
</table>

In 1984, Cooper et al. [56] carried out a randomized clinical trial demonstrating an increased prevalence of hypothyroid symptoms in individuals with SCH, including fatigue and weight gain. These results were later confirmed by cross-sectional [36,64] and case–control studies [66] in elderly hospitalized patients but individual symptom sensitivities were low.

Some studies have also assessed the presence of behavioral disorders – that is, cognitive dysfunction, psychological disorders, and depression – in SCH patients. The lifetime frequency of depression was significantly higher in SCH patients (56%) than in euthyroid individuals (20%) [65] and patients with SCH had significant memory impairment and differences in a psychological scale compared with controls [61].

Baldini et al. [66] studied two groups of female goitrous patients, one euthyroid and the other with SCH. A significant decrease in logical memory was found in SCH compared with euthyroid patients, whereas no impairment of affective functions was demonstrated. Gulseren et al. [67] studied 43 subjects with SCH and found that baseline scores for anxiety and depression were lower than in euthyroid patients and that L-thyroxine therapy improved these scores.

In contrast, very recently Jorde et al. [68] found no significant differences in cognitive function and hypothyroid symptoms between control subjects and those with SCH and in a large, well controlled study from the UK. SCH was not associated with depression, anxiety or cognition in the elderly [69].

**Risk of cardiovascular disease**

The cardiovascular system is an important target of thyroid hormone action [2,70,71] and is sensitive to slight variations in circulating thyroid hormone levels. The myocytes and the smooth muscle cells of the aorta and the coronary arteries share the pituitary cell’s ability to generate tri-iodothyronine from deiodination of thyroxine by type II 5’-monodeiodinase [72]. Tri-iodothyronine modulates the expression of proteins (the α- and β-isoforms of the myosin heavy chains, the sarcoplasmic reticulum Ca\(^{2+}\)-ATPase), and interferes in the expression of Na\(^+/K^+\)-ATPase, Na\(^+\)/Ca\(^{2+}\) exchange, and some K\(^+\) channels like Kv 1.5, Kv 4.2, and Kv 4.3 [2,68], which play a crucial role in the physiologic activity of myocytes. SCH may act directly on the heart, impairing both systolic and diastolic functions (Table 3); indirectly, SCH may increase cardiovascular risk by altering peripheral vascular resistance and serum lipid and coagulation profiles (Tables 3 and 4).

An early event in SCH-related cardiomyopathy, evaluated by Doppler echocardiography, is the impairment of...
diastolic function [73,74]. The diastolic dysfunction is caused by the reduced activity of sarcoplasmic reticulum Ca\textsuperscript{2+}-ATPase which controls the efficient concentration of calcium in the cytoplasm within the sarcoplasmic reticulum during diastole [2,73–75]. Both diastolic and systolic function during exercise are also impaired in SCH [73–75]. Others have [76] similarly reported diminished diastolic function by echocardiographic parameters in patients with SCH [76,77]. Finally, Ripoli et al. [78] demonstrated decreased cardiac-pump performance by MRI in SCH patients.

Recently, Sahin et al. [79] investigated the effect of SCH on sympathovagal balance and demonstrated that SCH modifies cardiac autonomic activity in SCH patients with serum TSH values ≥10 mIU/l, but not in those with TSH levels <10 mIU/l.

Caraccio et al. [80] measured oxygen uptake (VO\textsubscript{2}), carbon dioxide output, and heart rate during incremental step-up exercise in euthyroid subjects and patients with SCH. Maximal power output and VO\textsubscript{2 max} were reduced in SCH and the respiratory-quotient increments during work were significantly higher in SCH patients. Blood lactate, pyruvate, resting plasma free fatty acid and blood glycerol levels were significantly higher in patients than controls throughout baseline and exercise.

High blood pressure, mainly diastolic hypertension, has been documented in 20% of SCH patients compared with 3.4% in healthy euthyroid controls [81]. In SCH, endothelial dysfunction is present due to reduced NO availability and consequent arterial stiffness [82,83]. Patients with SCH have significantly higher carotid artery intima-media thickness values than age- and sex-matched controls. In contrast, Völzke et al. [84] reported diminished intima-media thickness in hypothyroid subjects and Cikim et al. [85] found no effect on intima-media thickness. Owen et al. [86\*] documented increased arterial stiffness in women with SCH compared with controls, as did Hamano and Inoue [87], who measured brachial-ankle pulse wave velocity. These results have recently been confirmed by Nagasaki et al. [88\*].

Coagulation parameters may be altered in SCH, contributing to increased cardiovascular risk. Gülü et al. [89] demonstrated that activities of factor VIII and von Willebrand factor were significantly lower in patients with SCH than in controls. Guldiken et al. [90] found that the global fibrinolytic capacity was significantly lower in patients with SCH than in controls, suggesting a relative hypercoagulable state in SCH.

Elevated C-reactive protein, l-arginine, asymmetric dimethylarginine concentrations, and insulin resistance, all risk factors for cardiovascular disease, may occur in patients with SCH [91,92].

Several studies have investigated the relationship between SCH, lipoprotein profile, and the risk of cardiovascular disease, with controversial results [93]. Some [30,94–97] demonstrated an increase in total cholesterol and low-density lipoprotein-cholesterol (LDL-C), apolipoprotein B, and lipoprotein (a) levels. SCH does not significantly affect high-density lipoprotein-cholesterol (HDL-C).

Table 4 summarizes the changes of the lipid profile observed in patients with SCH.

Table 4 Adverse effects of subclinical hypothyroidism on the lipoprotein profile

| Increased total cholesterol levels |
| Increased low-density lipoprotein-cholesterol levels |
| Increased apolipoprotein B levels |
| Increased lipoprotein (a) levels |

LDL-C levels are markedly elevated in overt hypothyroidism. Pearce and colleagues [98] have recently completed a study of patients with severe hypothyroidism and following restoration of normal TSH values with l-thyroxine administration. Lipids were analyzed by nuclear magnetic resonance when the patients were hypothyroid and again when euthyroid. The increase in LDL-C during hypothyroidism was due to an increase in concentrations of less atherogenic large LDL-C particles with no change in the concentrations of more atherogenic small and medium LDL-C particles.

The increase in total and LDL-C in hypothyroidism is due to a decrease in LDL receptor number [99,100]. Molecular mapping has revealed functional thyroid response elements in the promoter region of the LDL receptor gene [101]. Furthermore, several steps involved in lipid metabolism are impaired in SCH, and a direct influence of thyroid hormones on both cholesterol ester transfer protein and hepatic lipase, leading to a reduction of LDL clearance, has been reported [102].
Elevated plasma homocysteine has prothrombotic and proatherosclerotic effects [103,104] and is a modest independent predictor of coronary heart disease [105]. Elevated plasma homocysteine concentrations have been reported in patients with overt hypothyroidism, but not in those with SCH. Fasting homocysteine levels were within the normal range and did not change following L-thyroxine supplementation in patients with SCH [106,107].

The Whickam survey did not observe any association between SCH and coronary heart disease, dyslipidemia, or mortality over 20 years [40]. In contrast, an increased prevalence rate of atherosclerosis in elderly women with SCH has been documented in the Rotterdam study [37]. Among 1149 women aged 69±7.5 years in this population-based, cross-sectional study, women with SCH had a greater prevalence of aortic atherosclerosis (odds ratio, 1.7) and myocardial infarction (odds ratio, 2.3).

In a 10-year longitudinal study, SCH was associated in men, but not in women, with ischemic heart disease independent of age, systolic blood pressure, body mass index, cholesterol, smoking, erythrocyte sedimentation rate, or presence of diabetes [108]. There was no association, however, with cerebrovascular disease. By contrast, data from 3678 men and women enrolled in a Cardiovascular Health Study showed no differences between individuals with SCH and euthyroid subjects in the prevalence of angina, myocardial infarction, transient ischemic attack, stroke, or peripheral arterial disease [109].

In a cross-sectional study of nursing-home patients, Mya and Aronow [110] reported that SCH was associated with an increased prevalence of coronary artery disease and dyslipidemia. Walsh et al. [111] observed that 119 subjects with SCH, out of 2108 screened, had a significantly higher prevalence of coronary artery disease at baseline compared with euthyroid subjects (adjusted odds ratio, 1.8). Over a 20-year follow-up the risk for coronary heart disease and cardiovascular death were higher in the SCH subjects than in euthyroid subjects (hazard ratios, 1.7 and 1.5, respectively). This difference persisted even after adjustment for other cardiovascular risk factors.

Rodondi et al. [112] found that SCH was not associated with an increased risk for cardiovascular events, cardiovascular mortality, or all-cause mortality in a cohort of 2370 elderly participants in the Health, Aging, and Body Composition Study over 4 years of follow-up. In this cohort, there was an increased risk for the development of congestive heart failure in the SCH subjects (hazard ratio, 2.33), although this result was based on a relatively small number of events. Cappola et al. [113] reported that among 3233 participants in the Cardiovascular Health Study followed for up to 13 years, there was no increased risk for coronary heart disease, cerebrovascular disease, or cardiovascular or all-cause mortality. Finally, a very recent study by Pearce et al. [114] found no increased risk for cardiac events or mortality in the Framingham Heart Study cohort over a 20-year follow-up in the 281 of 4331 subjects with baseline TSH values of >5 mIU/l.

A recent meta-analysis of the effects of SCH on coronary heart risk reviewed 14 studies published up to 2004 and concluded that SCH increased the risk of coronary heart disease with an odds ratio of 1.65 [115].

Fertility and pregnancy
Basal and TRH-stimulated TSH concentrations were measured in 834 infertile women, and 20% had abnormal results [116]. Postcoital tests and spontaneous conception were significantly poorer in women with SCH than controls. Staub et al. [117] suggested that secondary hyperprolactinemia could be the cause of infertility in SCH women. In contrast, menstrual function in SCH patients and controls was similar in luteinizing hormone pulse patterns and 24-h mean serum luteinizing hormone, TSH, and prolactin concentrations [118].

Lincoln et al. [119] reported a 2.3% prevalence of elevated serum TSH concentrations in 704 women with infertility for at least 1 year. Eleven of 16 patients diagnosed with hypothyroidism had ovulatory dysfunction. TSH values were not determined in the control group, however.

Recently, Casey et al. [120] recruited 25 756 singleton pregnant women who had thyroid screening before 20 weeks of gestation and 2.3% had SCH. The relative risk for placental abruption was three times and that for preterm delivery 2-fold higher in women with SCH than euthyroid patients.

Stagnaro-Green et al. [121] screened 552 pregnant women for thyroglobulin antibody and TPO-Ab concentrations and 19.6% of these women had positive antibodies. Seventeen per cent of thyroid-autoantibody-positive women had a miscarriage, compared with 8.4% of the autoantibody-negative women. Miscarriage rates did not correlate with thyroid hormone levels, presence of cardiolipin autoantibodies, maternal age, gestational age at the time of the study, or previous obstetric history. The authors concluded that thyroid autoantibodies are an independent risk factor for miscarriage. In 2001, Abramson and Stagnaro-Green [122] reviewed the literature on the relationship between autoimmunity and miscarriage, and found that most studies reported a statistically significant increase in the incidence of thyroid autoantibodies in women with recurrent abortion.
as compared with controls [123–126]. Very recently, Negro et al. [127**] reported that untreated euthyroid women with TPO-Ab at the onset of pregnancy had miscarriage and premature delivery rates of 13.8 and 22.4%, respectively. These values were significantly higher than those observed in TPO-Ab-negative or euthyroid TPO-Ab-positive women who were treated with L-thyroxine. Vaquero et al. [128] studied recurrent aborters with SCH. Sixteen thyroid TPO-Ab-positive patients were treated with L-thyroxine and 11 patients received intravenous immunoglobulins. The thyroid autoantibody-positive women treated with L-thyroxine had more successful deliveries than the group treated with intravenous immunoglobulins (81.2 compared with 54.5%).

The detection of TPO-Ab in pregnant women during early gestation predicts an increased incidence of SCH during pregnancy and postpartum thyroid dysfunction [129]. Pregnant women with positive TPO-Ab and normal TSH values at the beginning of pregnancy developed a significant increase in serum TSH concentrations at term, reaching values of 3.5 mIU/l [127**]. Some studies have reported that SCH during pregnancy is associated with suboptimal intellectual performance and neurologic development in the offspring when tested during infancy and childhood [130–132]. It has been suggested that maternal serum free thyroxine concentrations are more sensitive than TSH values in predicting the likelihood of adverse intellectual outcomes in the offspring [133].

Subclinical hypothyroidism in newborns and children
Thyroid hormone deficiency is deleterious in infants, children, and adolescents because it causes growth delay, mental retardation, and precocious puberty in both sexes, and hirsutism in females. Iodine deficiency is the most common cause of hypothyroidism in children worldwide. In children living in iodine-replete areas, chronic autoimmune thyroid disease, X-ray treatment to the head and neck for malignant diseases, and drugs – in particular, carbamazepine and valproic acid – may induce SCH [134,135].

An important challenge during childhood is to diagnose SCH early when it is asymptomatic because it may cause irreversible damage when L-thyroxine-replacement therapy is delayed. A recent study [136] reported a 2.9% prevalence of thyroid autoantibodies in 8040 Sardinian schoolchildren living in areas with borderline iodine sufficiency or mild to moderate iodine deficiency. Seventy-seven (0.96%) children had serum TSH concentrations ranging between 5.2 and 32 mIU/l. As noted above, autoimmune thyroiditis and SCH are more common in children with type 1 diabetes mellitus [42].

Finally, an increased prevalence of SCH and more overt hypothyroidism due to autoimmune thyroiditis has been observed in children with Down’s and Turner’s syndromes compared with age-matched subjects [137,138].

Diagnosis
The clinical diagnosis of SCH is difficult to establish, especially in the elderly [139]. Some studies have indicated that the prevalence of symptoms and signs of hypothyroidism are increased in patients with SCH [60]. In contrast, other studies [140,141] have reported that some patients with serum TSH concentrations ranging between 5.6 and 379 mIU/l were judged euthyroid on clinical examination by expert endocrinologists.

A controversial subject is whether a screening program to detect hypothyroidism should be carried out, and if so, who should be screened. The ATA recommended screening both men and women, beginning at age 35 years and every 5 years thereafter [142]; the AACE recommended that only elderly patients, especially women, be screened [18]; the American Academy of Family Physicians recommended routine screening for patients older than 60 years of age [143]. The Endocrine Society, AACE and ATA jointly sponsored a consensus development conference [13], and found ’insufficient evidence to support population-based screening’; using US Preventive Services Task Force criteria [144,145] and, therefore, recommended ‘against population-based screening for thyroid disease’. The same societies reviewed the above conclusions and officially favored routine screening for subclinical thyroid dysfunction in adults, including pregnant women and those contemplating pregnancy [12]. This statement is reinforced by the fact that the costs of routine screening for SCH in subjects older than 35 years with a serum TSH measurement every 5 years are as favorable as other accepted preventive medical practices [146]. However, the above consensus statement was not universally accepted [11].

The role of TPO-Ab testing in the screening and/or diagnosis of SCH is another controversial question. Many societies, including the Royal College of Physicians [147], AACE, ATA, and Endocrine Society [12], suggest that measurement of serum TPO-Ab concentrations in patients with SCH be carried out since positive antibodies appear to predict the progression to overt hypothyroidism and may, therefore, favor treatment. Yet another set of guidelines, however, does not favor measurement of TPO-Ab in patients with SCH [13].

Treatment of patients with subclinical hypothyroidism
Whether all patients with SCH should be treated is a matter of debate. The Consensus Development Conferences sponsored by the Endocrine Society, AACE and
ATA [12,13] recommended beginning l-thyroxine substitutive therapy when TSH values exceed 10 mIU/l caused by adverse effects on serum lipids and the risk of progression to overt hypothyroidism. Therapy for milder forms of hypothyroidism (i.e. TSH levels <10 mIU/l) is controversial.

Some randomized clinical trials [56,57,148] suggest a beneficial effect of l-thyroxine therapy in patients with SCH. Some authors, therefore, recommend treating all patients with SCH [2,6,29,149]. Some recommend individualized management [150], whereas others strongly oppose l-thyroxine treatment in any SCH patient [7]. Unfortunately because many of the effects of SCH are subtle, adequately powered randomized clinical trials to definitively address this question may never be feasible.

Effects on symptoms/signs of hypothyroidism
Several studies have been performed to evaluate the effects of l-thyroxine replacement therapy on SCH symptoms. Results have been conflicting, showing statistically significant improvement [58,61,151,152], marginal improvement [56–58,66], or no benefit [57,59,60]. Furthermore, potential side effects of l-thyroxine overtreatment should always be considered. Indeed, iatrogenic thyrotoxicosis occurs in up to 20% of patients treated with l-thyroxine for hypothyroidism [30], potentially leading to more serious abnormalities than leaving SCH untreated [4,8].

In a recent study [153], patients who were at least 85 years old with elevated serum TSH concentrations surprisingly did not experience any adverse effects and had a prolonged life span. The treatment of elderly hypothyroid patients may be of limited benefit in clinical practice, however, this issue remains controversial.

Effects on the cardiovascular system
Beneficial effects of l-thyroxine-replacement therapy on cardiac function in SCH patients were first reported in 1981 [154]. Other trials have confirmed these observations [73], including improvement in the prejection/ejection ratio [76], and a reduction of the index of myocardial performance, isovolumic relaxation time, late mitral peak velocity, and heart rate during incremental step-up exercise [155].

In a small study of 14 SCH subjects and 28 euthyroid healthy controls, Taddei et al. [82] observed that 6 months of l-thyroxine-induced euthyroidism increased acetylcholine vasodilatation and normalized the basally low values of N\(^{02}\)-monomethyl-l-arginine (l-NMMA). As this compound is a nitric oxide synthase inhibitor, this study showed that l-thyroxine-replacement therapy reverses endothelial dysfunction resulting from a reduction in NO availability. Similarly, the increased arterial stiffness observed in SCH patients was reversed by l-thyroxine-replacement therapy [86*].

Effects on the lipid profile
The efficacy of thyroid-replacement therapy in reversing the abnormal lipid profile of SCH has been documented in several studies: a significant decrease in total cholesterol and LDL-C levels and a reduction of the intima-media thickness [156]. Lipoprotein (a) levels were not decreased, suggesting that altered lipoprotein (a) values reflect a genetic effect rather than decreased thyroid hormone action.

In the Basel Thyroid Study [58], the decrement of LDL-C during l-thyroxine therapy was greater in women with serum TSH concentrations exceeding 12 mIU/l. A significant decrease in apolipoprotein B-100 concentrations was also observed, whereas HDL-C, triglycerides, apolipoprotein AI, and lipoprotein (a) levels remained unchanged. In contrast, Kong et al. [59] found no changes in LDL-C levels in SCH patients following 6 months of l-thyroxine-replacement treatment.

Recently, Milionis et al. [157] observed that although l-thyroxine therapy did lower the increased LDL-C-associated human plasma platelet-activating factor acetylhydrolase activity to normal, it normalized the diminished HDL-C-associated platelet-activating factor acetylhydrolase activity in SCH subjects. The authors suggested that l-thyroxine-replacement therapy in SCH patients has potential antiatherogenic effects.

In a meta-analysis, Danese et al. [158] reported that l-thyroxine therapy for subjects with SCH, especially those with higher pretreatment cholesterol concentrations, lowered serum total cholesterol and LDL-C, but had no effect on HDL-C and triglyceride concentrations. A review by Inek and Ng [159] concluded that l-thyroxine treatment of SCH patients reduces LDL-C and total cholesterol, without affecting triglycerides.

Effects on fertility and pregnancy
Few trials on the efficacy of thyroid-hormone-replacement therapy in infertile and pregnant women with SCH have been conducted. l-Thyroxine treatment in infertile women with SCH resulted in successful pregnancies in 64% of women with ovulatory dysfunction, but not in those without a history of ovulatory dysfunction [119].

Hypothyroidism occurring during pregnancy is associated with impaired cognitive development in the offspring and increased fetal mortality. During pregnancy, especially in the first trimester when human chorionic gonadotropin, a weak TSH-receptor stimulator, is highest, maternal requirements of thyroid hormone increase. Pregnant women with SCH, therefore, should be promptly treated.
or the L-thyroxine dose should be increased if they are already taking L-thyroxine-substitution therapy for hypothyroidism prior to pregnancy [160].

Abalovich and coworkers [161] followed 114 women with primary hypothyroidism during 150 pregnancies. Most pregnancies were conceived when the women were euthyroid on adequate L-thyroxine-replacement therapy; however, 34% of the women were hypothyroid. When treatment with L-thyroxine was inadequate, miscarriage rates and premature delivery significantly increased. When treatment was adequate, all the overtly hypothyroid patients and 90.5% of the SCH patients had term deliveries and miscarriages did not occur.

Effects on newborns, children, and adolescents

Newborns with proven SCH should be treated with adequate doses of L-thyroxine within the first few weeks of life to prevent possible mental and growth retardation. Thyroid hormone can be withdrawn at approximately 1 year and thyroid function retested.

There is general agreement that children and adolescents with SCH should be adequately treated with L-thyroxine since significant improvement in height and development will occur [150]. Cetinkaya et al. [162] enrolled 2067 children with short stature and found that 39 subjects (0.19%) had SCH. When the anthropometric data of both prepubertal and pubertal patients were analyzed before and after 6–12 months of L-thyroxine-replacement therapy, both groups showed significant increases in growth velocity following L-thyroxine treatment. Finally, it has also been reported that the introduction of L-thyroxine-substitution therapy reduces the frequency of symptomatic hypoglycemia in pediatric patients with SCH and type 1 diabetes mellitus [163].

Thyroid-hormone-replacement therapy

L-thyroxine is the medication of choice in the treatment of hypothyroidism [164] and the daily dose of L-thyroxine needed to lower the serum TSH concentrations into the normal range is significantly less in older than in younger patients (50 compared with 100 μg/day). Recently, Roos et al. [165] concluded that a full starting dose of L-thyroxine in hypothyroid patients without cardiac diseases is safe and may be more convenient and cost-effective than a regimen with a low starting dose.

The administration of L-tri-iodothyronine in combination with L-thyroxine for the treatment of hypothyroidism should be questioned, since the large majority of circulating and tissue tri-iodothyronine derives from the peripheral outer-ring 5'-monodeiodination of thyroxine. Compared with L-thyroxine monotherapy, the combination therapy appeared to have beneficial effects on the mood, quality of life and psychometric performance in one study [166]. Escobar-Morreale et al. [167] conducted a systematic review of nine controlled clinical trials, including [166], comparing treatment with L-thyroxine alone with a combination of L-thyroxine and L-tri-iodothyronine in hypothyroid patients. Eight of the nine studies failed to show any difference between the two treatment regimens. Thus, L-thyroxine remains the best therapy for all forms of hypothyroidism.

Suggestions for L-thyroxine-replacement therapy

Figure 1 summarizes our suggestions regarding the indications to start L-thyroxine treatment in patients with SCH. L-Thyroxine therapy is occasionally indicated in patients with potentially reversible/ transient SCH (Table 1). Particular attention should be paid to women with postpartum thyroiditis. Many women with postpartum thyroiditis who develop SCH become euthyroid within 1 year following delivery, but some remain permanently hypothyroid [49–51]. In these patients, we advocate L-thyroxine-substitution therapy for approximately 1 year if symptomatic, with repeat thyroid-function tests approximately 2–3 months after L-thyroxine has been discontinued.

An underestimated cause of SCH is insufficient L-thyroxine doses to maintain euthyroidism; in these patients, the dose of L-thyroxine should be increased, and thereafter serum TSH concentrations should be monitored and the L-thyroxine dose tailored accordingly. Moreover, the problem of iodine deficiency, which may cause SCH, is still present in some countries, and it should be prevented and cured through adequate iodine prophylaxis.

L-thyroxine-replacement therapy should be started in subjects with SCH caused by conditions at high risk of progression to overt hypothyroidism (Table 1). The main controversy revolves around the upper limits of the serum TSH concentration beyond which substitutive therapy should be started. Patients with SCH should always be given thyroid-replacement therapy when serum TSH concentrations are persistently above 10 mIU/l. In SCH patients presenting with persistently elevated serum TSH concentrations less than 10 mIU/l, L-thyroxine-substitutive treatment should be started in the presence of at least one of the following conditions: pregnancy; childhood; elevated antithyroid autoantibody levels; evidence of hypoechoic thyroid gland on ultrasound; women with persistent infertility; diffuse or nodular goiter; or symptoms of hypothyroidism. In patients with a serum TSH above the normal range but below 10 mIU/l and who do not have any of these conditions, L-thyroxine therapy remains controversial.
Figure 1 Evaluation of patients with suspected subclinical hypothyroidism

Ab, antibody; ATD, antithyroid drugs; ESS, euthyroid sick syndrome; FT4, free thyroxine; L-T4, L-thyroxine; PPT, postpartum thyroiditis; ST, subacute thyroiditis; TSH, thyroid-stimulating hormone.

References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
•• of outstanding interest

6 McDermott MT, Ridgway EC. Subclinical hypothyroidism is mild thyroid failure and should be treated. J Clin Endocrinol Metab 2001; 86:4585–4590.
21 Andersen S, Brunn NH, Pedersen KM, Laurberg P. Biologic variation is important for interpretation of thyroid function tests. Thyroid 2003; 13:1069–1078.


This observational study used pulse wave analysis and tissue Doppler imaging to demonstrate that arterial stiffness was increased in patients with SCh and improved with l-tyroxine.


This observational study used pulse wave analysis and tissue Doppler imaging to demonstrate that arterial stiffness was increased in patients with SCh and improved with l-tyroxine.


89 Pearson EN, Wilson PWF, Braverman LE. Lipid subparticle size in overt hypothyroidism. American Thyroid Association 79th Annual Meeting; Phoenix, Arizona; 11–15 October 2006; Mary Ann Liebert, New Rochelle, NY; 2006; abstract 183.


This large, well-designed, prospective cohort study demonstrated that SCh at baseline is not associated with cardiovascular risk or mortality over a mean of 12.5 years of follow-up.


This small but innovative clinical trial demonstrated that L-thyroxine treatment in pregnant women with positive TPO-Ab significantly reduces risks for miscarriage and premature delivery.


Fatourechi V. Subclinical hypothyroidism: how should it be managed? Treat Endocrinol 2002; 1:211–216.


Cetrkayá E, Aslan A, Videnis S, Ocal G. Height improvement by l-thyroxine treatment in subclinical hypothyroidism. Pediatr Int 2003; 45:534–537.


This is a comprehensive review of the clinical studies addressing the efficacy of triiodothyronine in combination with l-thyroxine for the treatment of hypothyroidism.