

# The debate on treating subclinical hypothyroidism

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**ABSTRACT** Subclinical hypothyroidism (SCH) represents a mild or compensated form of primary hypothyroidism. The diagnosis of SCH is controversial, as its symptoms are non-specific and its biochemical diagnosis is arbitrary. The treatment of SCH was examined among non-pregnant adults, pregnant adults and children. In non-pregnant adults, treatment of SCH may prevent its progression to overt hypothyroidism, reduce the occurrence of coronary heart disease, and improve neuropsychiatric and musculoskeletal symptoms associated with hypothyroidism. These benefits are counteracted by cardiovascular, neuropsychiatric and musculoskeletal side effects. SCH is associated with adverse maternal and fetal outcomes that may improve with treatment. Treating SCH in children is safe and may improve growth. Importantly, the evidence in this field is largely from retrospective and prospective studies with design limitations, which precludes a conclusive recommendation for the treatment of SCH.

*Keywords:* adolescents, children, overt hypothyroidism, pregnancy, subclinical hypothyroidism

## DEFINITION AND DIAGNOSIS OF SUBCLINICAL HYPOTHYROIDISM

Subclinical hypothyroidism (SCH) is a condition characterised by a normal free thyroxine (FT<sub>4</sub>) level with an elevated thyrotropin (TSH) level.<sup>(1)</sup> It represents a mild,<sup>(2,3)</sup> compensated or preclinical form of primary hypothyroidism.<sup>(4)</sup> SCH may not be literally 'subclinical', as many individuals are symptomatic.<sup>(2,5)</sup> However, its symptoms can be non-specific, and the elderly are commonly asymptomatic for SCH.<sup>(6-9)</sup> Consequently, some studies have recommended diagnosing SCH biochemically.<sup>(10)</sup>

The biochemical diagnosis of SCH is controversial, as most definitions are arbitrary.<sup>(11)</sup> They are typically based on the condition that the TSH level exceeds the upper limit of the reference interval,<sup>(12)</sup> although TSH assays differ between studies.<sup>(13)</sup> Furthermore, Wartofsky and Dickey suspected that the reference interval of TSH may be lower than conventionally believed,<sup>(14)</sup> as it varies with ethnicity, geographic region, gender and pregnancy status.<sup>(15)</sup> TSH distribution curves also appeared to shift upward with increasing age.<sup>(16)</sup> Lastly, obesity may be a confounder in TSH measurement, although observational studies were inconsistent in this area.<sup>(17-20)</sup> Hence, the reference intervals for TSH based on age, gender, ethnicity, body mass index (BMI) and pregnancy status may need to be established before SCH can be clearly defined. SCH is commonly classified as mild when the TSH level is between 4.5 mIU/L and 10 mIU/L, and severe when TSH levels exceed 10 mIU/L in non-pregnant adults.<sup>(4,21)</sup>

TSH levels fluctuate and its elevation may be transient. Thus, the thyroid function test (TFT) should be repeated prior to diagnosing SCH, except in pregnant patients.<sup>(22,23)</sup> Additionally, it is essential to exclude other causes of elevated TSH, including the nocturnal measurement of TFT, recovery phase of non-thyroidal illness, hypothyroid phase of thyroiditis, assay variability or interference, untreated hypocortisolism,<sup>(24,25)</sup> pituitary thyrotrophoma, central hypothyroidism and TSH-receptor inactivation.<sup>(26)</sup> This is a review on the treatment of SCH in three

distinct populations: (a) non-pregnant adults; (b) pregnant adults; and (c) children.

## THE BENEFITS OF TREATING SUBCLINICAL HYPOTHYROIDISM IN NON-PREGNANT ADULTS

Treating SCH may be beneficial in non-pregnant patients with: (a) progression to overt hypothyroidism (OH); (b) coronary heart disease (CHD); (c) hypothyroid and neuropsychiatric symptoms; (d) musculoskeletal symptoms; and (e) other miscellaneous problems.

### Progression to overt hypothyroidism

SCH can progress to OH.<sup>(27)</sup> In prospective studies, the cumulative incidence of OH ranges from 33%–55% within 10–20 years in patients with SCH.<sup>(28-30)</sup> The annual rate of progression to OH in these patients ranges from 2%–6% within 5–6 years.<sup>(31,32)</sup> The risk factors for progression to OH include an initial TSH level exceeding 10 mIU/L,<sup>(29,33)</sup> elevated titres of thyroid peroxidase antibodies (TPOAb)<sup>(31,34)</sup> and the female gender. Conversely, SCH tends to resolve in TPOAb-negative subjects whose initial TSH levels are below 10 mIU/L.<sup>(29,31,32)</sup> It is uncertain if treating SCH prevents its progression to OH.

### Clinical outcomes of coronary heart disease

SCH is inconsistently associated with CHD. Prospective studies showed a higher incidence of CHD in SCH patients.<sup>(35-37)</sup> No association was found when TSH levels were below 7 mIU/L.<sup>(38)</sup> The incidence of heart failure (HF) was also found to be higher in prospective cohort studies of SCH patients.<sup>(39)</sup> A prospective cohort study by Rodondi et al demonstrated a positive correlation between TSH levels and HF risk, particularly when TSH levels exceeded 10 mIU/L.<sup>(40)</sup>

Interestingly, the association between SCH, CHD and HF may be influenced by age. A retrospective study revealed that SCH patients aged below 65 years had a greater prevalence of

CHD and all-cause mortality;<sup>(37)</sup> this was confirmed in meta-analyses of two prospective cohort studies.<sup>(41,42)</sup> A prospective observational study<sup>(6)</sup> and a subgroup analysis of the National Health and Nutrition Examination Survey (NHANES III) cohort<sup>(43)</sup> also showed better CHD outcomes in elderly SCH patients. In contrast, three prospective studies,<sup>(44-46)</sup> reported that SCH was not associated with CHD. Selmer et al suggested that SCH may protect patients against atrial fibrillation.<sup>(47)</sup> A retrospective cohort study by Razvi et al showed that patients between 40 and 70 years of age who were treated for SCH had lower hazard ratios for CHD events and all-cause mortality; no benefit was seen in patients beyond the age of 70 years.<sup>(48)</sup> Additionally, incident CHD, CHD mortality and the number of HF events were lower in the treatment groups in two prospective cohort studies.<sup>(35,40)</sup> Unfortunately, the Cochrane review<sup>(49)</sup> did not evaluate the effects of treatment on CHD outcomes.

### Surrogate measures of coronary heart disease risk

SCH is associated with surrogate measures of CHD risk, including echocardiographic measures of cardiac function, endothelial function, blood pressure (BP), lipid levels and various metabolic parameters. SCH was also associated with depressed systolic and diastolic ventricular function on echocardiography.<sup>(9)</sup> A placebo-controlled study by Monzani et al<sup>(50)</sup> and the Cochrane review<sup>(49)</sup> confirmed these findings, which improved with treatment. Reduced vasodilatation,<sup>(51)</sup> increased systemic vascular resistance and arterial stiffness<sup>(52)</sup> in SCH patients were reported in a randomised controlled trial (RCT) by Razvi et al.<sup>(53)</sup> Another RCT demonstrated increased carotid intima-media thickness (CIMT) in SCH patients.<sup>(54)</sup> Furthermore, treatment of SCH was shown to improve endothelial function,<sup>(53)</sup> CIMT<sup>(54,55)</sup> and homocysteinaemia.<sup>(56)</sup>

Hypertension was more common in SCH patients in two cross-sectional<sup>(57,58)</sup> and one prospective study.<sup>(35)</sup> Three studies showed no reduction of BP with treatment,<sup>(53,54,59)</sup> with the exception of Adrees et al's interventional trial.<sup>(56)</sup> Two studies,<sup>(5,35)</sup> which lacked statistical adjustment for age, and Monzani et al's RCT<sup>(50)</sup> reported that SCH patients had elevated total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) levels. The literature showed reduced TC and LDL-C levels with treatment of SCH.<sup>(53,54,56,60,61)</sup> Furthermore, in prospective interventional studies,<sup>(62,63)</sup> atherogenic lipid profiles improved with treatment of SCH, particularly in patients with severe dyslipidaemia and SCH. On the other hand, some RCTs showed no benefits for lipid profiles with treatment of SCH.<sup>(59,64-67)</sup> Finally, the Cochrane review and a systematic review reported a decreasing trend in lipid parameters with treatment of SCH.<sup>(49,68)</sup> In the literature, SCH was not associated with weight gain and metabolic syndrome.<sup>(17,69,70)</sup> Treating SCH did not reduce patient weight in many studies.<sup>(53,54,59,63,67)</sup>

### Hypothyroid and neuropsychiatric symptoms

SCH has been associated with mood disorders, a reduced quality of life<sup>(53,71)</sup> and treatment failure in depression.<sup>(72)</sup> However, this association was not seen in two cross-sectional studies<sup>(73,74)</sup>

and one prospective cohort study.<sup>(75)</sup> Most interventional trials showed no improvement in hypothyroid symptoms, quality of life and neuropsychiatric symptoms with treatment of SCH.<sup>(53,67,76,77)</sup> Meier et al showed improvement in mood, cognition and hypothyroid symptoms only when TSH levels exceeded 10 mIU/L.<sup>(60)</sup> Other interventional studies showed modest improvements in mood,<sup>(78)</sup> memory<sup>(66)</sup> and hypothyroid symptoms.<sup>(64)</sup> However, these were small RCTs of short durations. The Cochrane review concluded that treating SCH did not benefit mood, quality of life and hypothyroid symptoms.<sup>(49)</sup>

### Musculoskeletal symptoms

Reuters et al reported that weakness and myalgia were more prevalent in SCH.<sup>(79)</sup> Brennan et al showed that SCH was also associated with reduced muscular strength.<sup>(80)</sup> However, two prospective cohort studies, by Simonsick et al and Virgini et al, showed no associations between SCH and musculoskeletal symptoms.<sup>(8,81)</sup> Furthermore, physical function appeared to be better in elderly subjects with SCH.<sup>(9)</sup> There were conflicting reports on fracture rates from prospective cohort studies by Lee et al and Svare et al.<sup>(82,83)</sup> Brennan et al<sup>(80)</sup> showed improvement in strength measurements, while Mainenti et al<sup>(84)</sup> showed improvement in cardiopulmonary performance with treatment.

### Other manifestations of subclinical hypothyroidism

A prospective trial associated impaired gastric motility with SCH in premenopausal women.<sup>(85)</sup> A cross-sectional study by Chung et al showed a linear relationship between non-alcoholic fatty liver disease and SCH.<sup>(86)</sup> RCTs by Cinemre et al and Ravanbod et al showed that the treatment of SCH led to better correction of iron deficiency anaemia,<sup>(87,88)</sup> while that by Christ-Crain et al did not.<sup>(89)</sup> A Korean prospective interventional study by Shin et al found that treating SCH slowed the progression of chronic kidney disease.<sup>(90)</sup> However, these trials were small and the reported benefits require replication in larger trials.

## RISKS OF TREATING SUBCLINICAL HYPOTHYROIDISM IN NON-PREGNANT ADULTS

Overtreatment of SCH can cause complications and symptoms of thyrotoxicosis<sup>(27)</sup> have been reported. Nervousness and anxiety were reported by Nyström et al<sup>(65)</sup> and Kong et al.<sup>(67)</sup> Some subjects "felt worse" following treatment in a placebo-controlled study by Cooper et al.<sup>(64)</sup> Tachyarrhythmias and angina pectoris were also reported by Nyström et al<sup>(65)</sup> and Jaeschke et al.<sup>(66)</sup> Low bone mass and fractures are also potential complications of treatment.<sup>(91)</sup> Conversely, many RCTs demonstrated the safety of thyroxine for the treatment of SCH, as no participants reported adverse effects, required dose reduction or withdrew from the studies.<sup>(53,59,76,92)</sup> The Cochrane review<sup>(49)</sup> noted that only four studies reported adverse outcomes with the treatment of SCH, and none showed significant associations between treatment and adverse outcomes. However, these studies were poorly designed and underpowered. As evidence is lacking, the United States Preventive Services Task Force<sup>(1)</sup>

and the Cochrane review made no specific recommendations in this regard.

## SUBCLINICAL HYPOTHYROIDISM IN PREGNANCY

The diagnosis of SCH differs slightly in pregnant patients. Firstly, the symptoms of pregnancy mimic hypothyroidism,<sup>(5)</sup> mandating the biochemical diagnosis of SCH. Secondly, gestational changes in the hypothalamic-pituitary-thyroid axis interfere with the measurement of FT<sub>4</sub> by conventional assays.<sup>(93,94)</sup> Consequently, an emphasis is placed on TSH measurement, for which guidelines recommend establishing local trimester-specific reference intervals.<sup>(95,96)</sup> Lastly, the diagnostic threshold for SCH in pregnancy differs from that in non-pregnant adults. Using trimester-specific reference intervals, the American Thyroid Association (ATA) and Endocrine Society<sup>(96)</sup> recommend the following thresholds for TSH level: (a) between 0.1–2.5 mIU/L in the first trimester; (b) between 0.2–3.0 mIU/L in the second trimester; and (c) between 0.3–3.5 mIU/L in the third trimester.

### Maternal outcomes

It has been debated whether SCH leads to adverse maternal outcomes. A prospective cohort study by Casey et al on 25,000 pregnancies showed a higher incidence of placental abruption and preterm delivery in patients with SCH.<sup>(97)</sup> An association with miscarriages was demonstrated in cohort studies by Benhadi et al and Allan et al<sup>(98,99)</sup> and prospective trials by Negro et al and Liu et al;<sup>(100,101)</sup> Wilson et al reported significantly higher preeclampsia rates in the SCH cohort.<sup>(102)</sup> A small cohort study by Leung et al, involving 68 pregnancies, showed an association between SCH and gestational hypertension (including pregnancy-induced hypertension, preeclampsia, and eclampsia).<sup>(103)</sup> These adverse maternal outcomes were reaffirmed in two meta-analyses by Reid et al and Thangaratinam et al.<sup>(104,105)</sup> However, Cleary-Goldman et al did not find an association between SCH and maternal adverse outcomes in their prospective cohort study involving 10,000 pregnancies.<sup>(106)</sup> The adverse outcomes that were measured included preterm labour, macrosomia, gestational diabetes mellitus and preterm premature rupture of membranes.<sup>(106)</sup>

### Fetal outcomes

The adverse outcomes of SCH in the fetus include perinatal morbidity and mortality, as well as subsequent neurologic and psychomotor delays. Saki et al's study on 600 pregnancies associated SCH with intrauterine growth retardation and low Apgar scores.<sup>(107)</sup> A cohort study on 2,500 pregnancies found a significantly higher prevalence of neonatal respiratory distress and intensive care unit admissions.<sup>(98)</sup> Smit et al<sup>(108)</sup> showed delayed neurologic development in children born to mothers with SCH. However, this study only included 20 subjects, and psychomotor testing was conducted variably from the ages of 6–24 months.<sup>(108)</sup> Subsequently, Li et al confirmed poorer intellectual and motor development in children aged 25–30 months who were born to mothers with SCH during pregnancy.<sup>(109)</sup> Additionally, Haddow et al demonstrated lower intelligence quotient (IQ) scores in

the offspring (aged 7–9 years) of SCH mothers in a cohort study involving 25,000 subjects.<sup>(110)</sup> Worryingly, Ajmani et al's study on 400 women reported adverse maternal and fetal outcomes in SCH.<sup>(111)</sup> Conversely, Lazarus et al showed no cognitive impairment in children whose mothers had SCH during pregnancy.<sup>(112)</sup> However, this study was limited, as it measured cognition using different IQ tests at different ages; furthermore, different TSH assays were used between the centres.

### Controversy over treatment during pregnancy

The arguments for treating SCH during pregnancy include a reduction in obstetric and neonatal complications, as seen in the RCT by Negro et al,<sup>(113)</sup> and an improvement in miscarriage and live birth rates in women undergoing assisted reproductive techniques.<sup>(114)</sup> On the other hand, the RCT by Lazarus et al showed no cognitive benefits in the offspring of mothers who were treated.<sup>(112)</sup> In light of the conflicting and limited evidence, the Cochrane review did not reach a conclusion on this issue.<sup>(49)</sup> The ATA recommended treating SCH if TPOAb titres are elevated<sup>(95)</sup> and made no recommendations for TPOAb-negative subjects. However, it opined that treatment is reasonable in a woman at risk for SCH complications. Arguably, treatment of SCH in pregnant women may be proposed, as the associated cost and risks are low. A clear discussion with the patient, stating the pros and cons of treatment (and lack of treatment), is advised.

## SUBCLINICAL HYPOTHYROIDISM IN CHILDREN AND ADOLESCENTS

The definition and adverse outcomes of SCH in children and adolescents are similar to those in adults.<sup>(4)</sup> Among children and adolescents in the NHANES III cohort, 1.7% had SCH,<sup>(115)</sup> while other studies report a prevalence up to 9.5%.<sup>(116)</sup>

### Progression to overt hypothyroidism

Based on prospective studies, the majority of children and adolescents with SCH do not progress to OH.<sup>(117)</sup> In the prospective studies conducted on children with goitre<sup>(118)</sup> and autoimmune thyroiditis,<sup>(119,120)</sup> between 5.6%–50% of patients progressed to OH. Wasniewska et al studied children with no identifiable aetiologies for their SCH; 20.4% of them progressed to OH.<sup>(121)</sup>

Several factors may predict the progression of SCH to OH. In a retrospective analysis of 120,000 children, Lazar et al found a greater occurrence of OH in children with initial TSH levels above 7.5 mIU/L and those who were female.<sup>(122)</sup> Radetti et al found that on initial presentation, goitre and elevated antithyroglobulin antibody titres predicted the progression to OH; on follow-up, rising TPOAb titres and TSH levels were also found to be risk factors for progression.<sup>(123)</sup> Lastly, Wasniewska et al found an association between prepubertal status at diagnosis and progression to OH.<sup>(121)</sup>

### Skeletal development

Two studies by Cerbone et al<sup>(124)</sup> and Di Mase et al<sup>(125)</sup> reported the lack of impact of SCH on skeletal growth and maturation in children. Cerbone et al found no significant difference in the

growth, bone maturation and BMI of 36 children with SCH who were matched with controls.<sup>(124)</sup> Similarly, Di Mase et al reported no differences in the lumbar spine bone density and phalangeal quantitative ultrasonography in 25 children with SCH.<sup>(125)</sup>

### Intellectual development and puberty

SCH does not appear to impact cognitive development in children. Cerbone et al described no relationship between TSH levels and IQ or behaviour in children with SCH.<sup>(124)</sup> Verbal fluency and encoding test scores were also not affected by SCH in another case-control study by Ergür et al.<sup>(126)</sup> Pubertal delay was not found to be associated with SCH by Cerbone et al and Rapa et al.<sup>(124,127)</sup>

### Cardiovascular risk factors

SCH was associated with hypertension in children and adolescents in two cross-sectional studies by Chen et al and Ittermann et al.<sup>(128,129)</sup> Furthermore, triglyceride levels, homocysteine levels and waist-to-hip ratios were higher in children with SCH compared to controls in another cross-sectional study by Cerbone et al, which also found that high-density lipoprotein cholesterol was lower in SCH patients.<sup>(130)</sup>

### Migraine

The association between SCH and migraines is controversial. Small cross-sectional studies by Fallah et al and Ekici et al offered conflicting results in this regard.<sup>(131,132)</sup>

### Treating children and adolescents

In children and adolescents, the treatment of SCH does not appear to confer benefits. A retrospective study reported improvement in growth velocity following thyroxine therapy. However, this prospective study was conducted among type 1 diabetes mellitus patients. An observational study by Aijaz et al, conducted over eight weeks, reported no effects on the neuropsychological function of children,<sup>(133)</sup> although this study had methodological flaws. Treatment does not prevent progression to OH.<sup>(134)</sup> In their review, De Luca et al found no improvement in growth and bone maturation, BMI and cognitive function with treatment of SCH.<sup>(135)</sup> Cetinkaya et al<sup>(136)</sup> reported no treatment side effects. However, in a prospective study by Eyal et al that was conducted in the United States, 12.5% of children were over-treated.<sup>(137)</sup> Rother et al and Svensson et al reported a reduction in goitre size with treatment.<sup>(138,139)</sup>

As the evidence is limited, the ATA recommends against treating SCH in children with a TSH level of 5–10 mIU/L. It recommends treating SCH in children when: (a) the TSH level exceeds 10 mIU/L; (b) the child is symptomatic; or (c) the child is at risk for OH. Additionally, treatment may be considered if a goitre is present, the child is TPOAb-positive or when growth is compromised.<sup>(140)</sup>

### CONCLUSION

The treatment of SCH is highly controversial. These controversies may be clarified when the results of the Thyroid Hormone Replacement for Subclinical Hypothyroidism study, an ongoing

multi-centre European RCT, are published. For now, the treatment decision needs to be individualised. Treatment may be considered if: (a) symptoms are present; (b) there is a goitre; (c) there is risk of progression to OH; (d) there are risks of CHD, particularly in patients younger than 70 years of age; or (e) TSH levels exceed 10 mIU/L. Furthermore, SCH should be identified accurately (if possible) and treated adequately in pregnant women, lactating mothers, neonates and children. This is because unidentified and untreated SCH in these populations may lead to dire consequences.

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