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# Subclinical hypothyroidism in children: updates for pediatricians

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Subclinical hypothyroidism (SH) is defined as serum thyroid-stimulating hormone (TSH) above the upper limit of the reference range in the presence of normal free T4 concentrations. Depending on the degree of TSH elevation, SH could be defined as mild (TSH, 4.5–10 mIU/L) or severe (TSH>10 mIU/L). While there is a general consensus to treat children with serum TSH levels above 10 mU/L, the management of the mild form is uncertain and should be individualized. In this mini-review, we present a brief review of SH in children based on extensive literature review and long-standing clinical experience. This review provides the prevalence, causes, clinical presentation, consequences, investigation, and up-to-date therapeutic approach of SH in children. Generally, the purpose of the review is to provide pediatricians with an update of this common and continuously evolving condition.

Keywords: Subclinical hypothyroidism, Hashimoto's thyroiditis, Thyroid-stimulating hormone, Thyroid autoantibodies, Levothyroxine

## Highlights

Subclinical hypothyroidism (SH) is defined as serum levels of thyroid-stimulating hormone (TSH) above the upper limit of the reference range in the presence of normal concentrations of free T4. Hashimoto's thyroiditis (HT) is the most common cause of SH, especially among older children and adolescents (age range, 8–18 years). While there is an agreement to treat children with serum TSH levels above 10 mU/L, the treatment of the mild form (TSH levels between 4.5 and 10 mU/L) is uncertain and should be individualized.

## Introduction

Subclinical hypothyroidism (SH) is a biochemical situation characterized by serum thyroid-stimulating hormone (TSH) levels above the upper limit of the reference range for the assay with free T4 (fT4) values within the reference interval of the assay.[1] This condition is also known as compensated hypothyroidism or isolated hyperthyrotropinemia. SH is considered to be a mild form of thyroid failure by some investigators due to the inverse log-linear relationship between TSH and thyroid hormones.[2] Depending on the degree of TSH elevation, SH could be classified as mild (TSH, 4.5–10 mIU/L) or severe (TSH>10 mIU/L).[3]

## Epidemiology

SH prevalence in adults is reported to be 4%–20% and is higher in females, in the elderly, and in whites.[4] SH in children is less common, with a prevalence that has been reported to range around 1.7%.[5]

## Etiology

### 1. Hashimoto's thyroiditis

Hashimoto's thyroiditis (HT) is the most common cause of SH, especially among older children and adolescents (age range, 8–18 years).[6] HT is characterized by the existence of thyroid autoantibodies (antithyroid peroxidase [TPO Ab] and antithyroglobulin [TG Ab]) with or without goiter.[7] Patients with HT may develop subclinical or overt hypothyroidism depending on the intensity of the immunological injury.[8]

### 2. Genetic mutations and genetic syndromes

#### 1) Mutations in the TSH-receptor
Heterozygous mutations in the gene encoding TSH-receptor have been reported in 11.4%–29.0% of children with nonautoimmune SH.[9,10] These mutations are associated with a wide range of thyroid dysfunction, from severe congenital hypothyroidism due to thyroid hypoplasia to SH.[11]

#### 2) Dual oxidase 2 mutations
Mutations in the gene encoding dual oxidase 2 (*DUOX2*) are associated with defects in iodide organification and are also reported to cause persistent SH.[12]

#### 3) Down syndrome
A high prevalence of SH has been associated with Down syndrome (DS) ranging from 25.3% to 60.0%.[13] HT is more likely to present with SH in DS compared to the general population.[14]

#### 4) Turner syndrome
In patients with Turner syndrome, SH is also frequent, with a prevalence of up to 58%, and is mainly related to the presence of HT.[15]

### 3. Persistent neonatal hyperthyrotropinemia

A lower TSH cutoff at neonatal screening may result in an increased incidence of both mild and transient forms of hypothyroidism. In the neonatal period, SH can be defined by a TSH value between 6 and 20 mIU/L and normal FT4 levels.[16] SH in the neonatal period is more common in some high-risk babies such as preterm or sick neonates, small for gestational age infants, neonates born after *in vitro* fertilization, and infants from multiple pregnancies. Other causes of SH include syndromic babies, those with congenital anomalies, corticosteroid treatment during pregnancy or in the neonatal period, and maternal thyroid abnormalities.[17]

### 4. Obesity

Studies indicate that SH may be detected in around 10%–23% of children with obesity.[18] SH seems to be a sequela, rather than a cause of weight gain. Accordingly, several studies have documented that TSH levels normalized after participation in weight-loss programs.[19]

### 5. Iron deficiency anemia

Gökdeniz et al.[20] reported that 16.6% of children with iron deficiency anemia (IDA) had SH, and Metwalley et al.[21] reported that primary school children with IDA were prone to develop SH and intellectual dysfunction.

### 6. Nephrotic syndrome

Afroz et al.[22] reported that children with Nephrotic syndrome (NS) commonly experience a state of SH during the active phase of proteinuria without symptoms of hypothyroidism. NS may trigger the onset of hypothyroidism or aggravate pre-existing SH, increasing requirements of L–T4 supplementation because of urinary loss of free and protein-bound thyroid hormones.[23]

### 7. Idiopathic SH

Children with SH without clear etiology are classified as having idiopathic SH.[24] In most cases, however, thyroid function remains relatively stable for long periods with a lower risk of deterioration in thyroid function over time.[25]

### 8. Iodine deficiency or excess

Low iodine intake for a prolonged period may result in mild to severe SH, as well as goiter and overt hypothyroidism.[26] Additionally, population studies indicate that SH may also occur in subjects with high iodine intake.[27]

### 9. Ionizing radiation

Children exposed to ionizing radiation either by therapy or in the environment may be susceptible to developing SH.[28]

### 10. Medications

Amiodarone[29] and interferon (IFN)-α[30] are examples of drugs that may impair thyroid function, causing SH. Additionally, SH is frequently reported in children treated with antiepileptic drugs (valproic acid, phenytoin, carbamazepine, and phenobarbital).[31]

### 11. Euthyroid sick syndrome

A child with acute illness may have a transient decrease in thyroid hormone secretion. During the recovery stage, a transient increase in TSH is the normal mechanism for restoring normal thyroid hormone levels, and TSH will return to normal

within a short period of time.[32)] Thus, TSH levels should be measured at a 2- to 3-month interval to rule out laboratory error or transient increase in TSH levels.[33)]

## 12. Laboratory pitfalls

High TSH levels with normal fT4 may result from laboratory interference.[34)] Six main types of interference in thyroid function testing have been identified: macro-TSH, biotin, antistreptavidin antibodies, antiruthenium antibodies, TH autoantibodies, and heterophilic antibodies.[35)] Macro-TSH is characterized by high-molecular-weight complexes of TSH (mainly bound to IgG) with low bioactivity that accumulate in the circulation because of slow clearance and can be recognized by available immunoassays as hyperthyrotropinemia. Patients with macro-TSH have elevated serum TSH and normal FT4 levels similar to SH.[36)]

## 13. Physiological variation

SH levels in normal children tend to vary during the day as well as over time.[37)] TSH secretion follows circadian rhythms with the lowest level in the late afternoon and highest level between midnight and 4 AM.[38)] In adolescent females, a transient increase in TSH levels may occur during the midmenstrual cycle.[39)] Moreover, sleep deprivation may be associated with elevated TSH.[40)]

## Clinical manifestations

The clinical manifestation of SH may vary from no manifestations to full-blown thyroid dysfunction. This may be related to age, the sensitivity of patients to thyroid hormone

**Table 1. Work up of subclinical hypothyroidism in children**

History
  • Birth history
  • Family history of autoimmune disease
  • Genetic disorders
  • History of radiation
  • Drugs
  • Iodine excess or deficiency
  • Symptoms of hypothyroidism
Physical examination
  • Goiter
  • Growth parameters (weight, height, and body mass index)
  • Vital signs (heart rate and blood pressure)
  • Signs of hypothyroidism
  • Syndromic features
Investigations
  • Routine laboratory test
  • Follow-up of thyroid function test
  • Thyroid autoantibodies
  • Thyroid ultrasound
  • Lipid profile

deficiency severity, and the duration of SH.[5)] The abnormalities most frequently associated in the pediatric population are goiter, weight gain, sleepiness, weakness, anemia, and increased cholesterol levels.[1)] The severity of symptoms is not always strictly associated with TSH levels.[7)]

## Workup and diagnosis (Table 1)

SH diagnosis requires measurement of serum TSH and fT4.[3)] Confirmatory assay of TSH and fT4 should be performed within 2–3 months.[5)] The presence of thyroid autoantibodies (TPO Ab and/or TG Ab) and/or the demonstration of a hypoechoic pattern of the gland by ultrasound assist in the diagnosis of HT. The typical ultrasound pattern may be present before the appearance of thyroid antibodies.[41)] Thyroid ultrasound has been established as a useful tool in the investigation of persistent SH, especially when no clear causes are identified. Furthermore, high TSH levels in children with a thyroid nodule may be used as a predictor of thyroid malignancy; therefore, thyroid ultrasound examination is an important tool in the follow-up of both treated and untreated SH patients.[1,42)]

## Consequences of long-standing untreated SH in children

### 1. Cardiac functions

SH in children has been reported to be associated with an increased risk of hypertension.[43)] Regarding ventricular function in children with SH, recent studies have revealed conflicting results.[44)]

### 2. Endothelial function and epicardial fat thickness

Endothelial dysfunction is an early and reversible event of vascular affection and has been used to predict future coronary artery disease prior to atherosclerotic changes.[45)] Flow-mediated dilation (FMD) is a noninvasive ultrasound method currently recognized as a useful technique for the evaluation of endothelial function.[45)] Moreover, epicardial fat thickness (EFT) is a sensitive and reliable marker of cardiovascular risk and has become an emerging target for medical interventions.[46)] Only one study that we are aware of, conducted by Farghaly et al.,[47)] has evaluated FMD and EFT. Their evaluation included 32 children with mild SH caused by HT. The authors reported higher EFT and lower FMD in the studied children compared with controls, and EFT was associated with FMD responses.

### 3. Lipid profile

Among children with untreated SH, mild abnormalities in lipid profile have been reported in the form of slight decreases in high-density lipoprotein-cholesterol (HDL-C) and mild increases in triglyceride/HDL-C ratio.[48)] In addition, a higher

atherogenic index has been reported by Farghaly et al.[47] in children with mild SH caused by HT.

### 4. Insulin resistance

The current studies regarding the relationship between SH and insulin resistance provide contrasting results.[48]

### 5. Cognitive function

The available data on cognitive function in children with SH showed that cognitive scores, attention level, and verbal fluency were affected in children with SH.[49]

### 6. Growth and bone density

SH has been reported not to be associated with alterations in growth, bone mineral status and bone maturation in children.[49]

## The natural history of SH

Predictors of progression to overt hypothyroidism include increasing age, female gender, presence of goiter, presence of positive TPO Abs, high TSH levels at diagnosis, family history of autoimmune thyroid disease, and the presence of other autoimmune conditions (i.e., celiac disease) or genetic syndromes (i.e., DS and TS).[14,15] The most important factor affecting the natural history of SH is its etiology.[3]

## Treatment (Table 2)

Disagreement exists over whether to treat children with SH and the cutoff point to use for the decision to treat.[1] The optimal management of SH children should take into consideration the age of the child, clinical and biochemical abnormalities, the degree of increase of TSH level, the etiology, duration of thyroid dysfunction, and the presence of syndromes. Management should be individualized.[5] Approval for treating children with serum TSH levels higher than 10 mU/L has been issued. This approval is irrespective of etiology and applies especially to children with HT and progressive worsening of thyroid function over time. However, treatment of mild forms of SH (TSH, 4.5–10 mU/L) is uncertain and should be individualized.[5] In subjects with mild SH without symptoms or signs of hypothyroidism, regular assessment of TSH and fT4 levels every 6 months and thyroid autoantibodies and thyroid ultrasound yearly are recommended. This is particularly necessary for those with chromosomal abnormalities (TS and DS) or autoimmune disorders with the increased risk of progression into overt hypothyroidism.[5]

In neonates, if venous TSH levels are persistently above 20 mIU/L with normal fT4 levels, initiation of L–T4 treatment is advisable. However, if TSH levels are between 6 and 20 mIU/L with normal fT4 levels, the decision to start treatment should be individualized.[16,17] In children with IDA associated with SH, studies have reported that children with TSH levels >10 mIU/L may benefit from L–T4 treatment which provides a desirable treatment response to iron replacement.[20] In children with NS combined with SH, L–T4 therapy may be used to avoid deterioration of thyroid function and development of overt hypothyroidism and to alleviate the deleterious effect of thyroid hormone deficiency on body homeostasis and development of overt hypothyroidism.[23] Treatment with L–T4 should be advised for children using medications, such as antiepileptic medications and IFN α, with a TSH level >10 mIU/L until drugs are stopped.[30,31] Last, children with persistent SH and diffuse or nodular goiter should be treated with L–T4 replacement with the aim of normalizing serum TSH levels to protect against the development of thyroid carcinomas.[50]

## Conclusions

SH is a common disorder in children most frequently caused by HT. However, genetic mutations, IDA, drugs, NS, idiopathic SH, and obesity are important causes of SH in children. While there is approval to treat children with serum TSH levels above 10 mU/L, the treatment of the mild form (TSH levels between 4.5 and 10 mU/L) is uncertain and should be individualized.

## Conflicts of interest

No potential conflict of interest relevant to this article was reported.

**Table 2. Recommendation of treatment with L–T4 in children with SH**

| |
|---|
| 1. Children with SH with TSH levels higher than 10 mU/L, irrespective of its etiology. |
| 2. Children with SH with TSH levels 4.5–10 mU/L: |
|   Goiter |
|   Signs or symptoms of hypothyroidism |
|   Increased risk of progression into overt hypothyroidism |
|    -HT |
|    -Syndromic children (DS, TS) |
|    -Genetic etiology |
|   Thyroid nodule, nodular goiter |

SH, subclinical hypothyroidism; TSH, thyroid-stimulating hormone; DS, Down syndrome; TS, turner syndrome; HT, Hashimoto's thyroiditis.

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