Subclinical Hypothyroidism in Children: Approach Protocol Proposed by the Sociedade de Endocrinologia e Diabetologia Pediátrica of Sociedade Portuguesa de Pediatria

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Introduction

Subclinical hypothyroidism, also known as isolated hyperthyrotropinemia, is defined as serum thyroid stimulating hormone (TSH) concentrations above the upper limit of the reference range, in the presence of normal concentrations of free thyroxine (FT4) and total thyroxine (T4). This is a purely biochemical definition and, following the neonatal period, a serum TSH concentration above 5 mUI/L can usually be considered abnormal.[1-3] It should be noted, however, that serum levels of thyroid hormone may vary depending on age and, to some extent, the method used to measure them. Table 1 presents one example of reference values widely accepted.[4,5]

Due to the wide variability of TSH concentrations among healthy individuals and different biochemical methods, the presence of two independent TSH measurements above the expected range, with normal FT4 levels, is necessary to define subclinical hypothyroidism.[3,6]

Subclinical hypothyroidism can be classified as mild (TSH above the upper limit for age but below 10 mUI/L) and severe (TSH $\geq$ 10 mU/L)[3,6,7] or, in terms of etiology, as idiopathic or secondary.[8]

There has been an increase in the detection of subclinical hypothyroidism cases, as a result of screenings carried out in cases such as obesity, short stature, and psychomotor development delay.[2,9] Thyroid function screening is recommended in asymptomatic patients who present certain risk factors, such as[10]:

1. Autoimmune diseases (AID), namely type 1 diabetes mellitus, celiac disease, and vitiligo;
2. Chromosomal disorders (trisomy 21, Turner syndrome);
3. Iodine deficiency (due to living in iodine-deficient areas);
4. Treatment with drugs that interfere with thyroid hormones (valproic acid, phenytoin, lithium, amiodarone).

Subclinical hypothyroidism is estimated to occur in 1.7%-2.9% of the pediatric population,[1,6] with severe cases occurring in only 0.4%.[11] Subclinical hypothyroidism represents a significant number (about 4%) of pediatric endocrinology referrals.[1]

Etiology

In terms of etiology, subclinical hypothyroidism is identical to overt hypothyroidism, the main cause being chronic autoimmune thyroiditis also known as Hashimoto's thyroiditis (Table 2).[3,6,12]

Table 1. Thyroid stimulating hormone, free and total thyroxine serum levels, according to age[4,5]

Age	Thyroid stimulating hormone (mU/L)	Free thyroxine (ng/dL)	Total thyroxine (µg/dL)
1-12 months	0.6-7.3	0.9-2.3	7.2-15.7
1-5 years	0.7-6.6	0.8-1.8	6.4-13.5
6-10 years	0.8-6.0	1.0-2.1	6.0-12.8
11-18 years	0.6-5.8	0.8-1.9	4.7-12.4
> 18 years	0.4-4.2	0.9-2.5	5.3-10.5

Adapted from: Yebra Yebra J, Oliva Pérez P, Gómez Llorente JL, Guerrero-Fernández J. Disfunción tiroidea. Interpretación de las pruebas tiróideas. In: Guerrero-Fdez J, González Casado I, Barreda Bonis AC, Itza Martín N, Mora Plama C, eds. Manual de diagnostico y terapeutica en endocrinologia pediatrica. Madrid: Ergon; 2018,[4] and Ross DS. Laboratory assessment of thyroid function. http://www.uptodate.pt.[5]

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Table 2. Etiology of hyperthyrotropinemia[3,6,12]

Hashimoto's thyroiditis	Main cause of subclinical hypothyroidism, especially in children aged between 8 and 18 years and those with trisomy 21 and Turner syndrome and other autoimmune diseases, such as celiac disease or type 1 diabetes mellitus.
Persistent neonatal hyperthyrotropinemia	More frequent in preterm, small for gestational age, post-*in vitro* fertilization cases and associated with morphological alterations of the thyroid gland or genetic causes in about 30% of cases.
Genetic	Heterozygous mutations of the TSH receptor gene have been identified in 11%-29% of idiopathic subclinical hypothyroidism. In trisomy 21 patients, subclinical hypothyroidism occurs in 25% to 60%, and it can be autoimmune or not. Pseudohypoparathyroidism type 1A (pseudohypoparathyroidism type 1A, Albright's osteodystrophy), the mutation in the *Gs*α gene, which regulates the signaling pathway linked to cyclic adenosine monophosphate, causes resistance to multiple hormones, namely PTH and TSH.
Iodine deficiency/excess	Rare. Excessive consumption as well as iodine deficiency can lead to subclinical hypothyroidism, usually associated with goiter.
Drugs	Most commonly alfa interferon, antiepileptics (valproate, phenobarbital, phenytoin, carbamazepine), lithium, and amiodarone.
Exposure to ionizing radiation and contrast products	Especially after irradiation, before bone marrow transplantation, in children under nine years of age. Of these, 26% will develop subclinical hypothyroidism, which is usually transitory. Exposure to iodinated contrast may increase the risk (2-6 times) of developing subclinical hypothyroidism, although the duration and impact of this dysfunction are unknown.
Neuroendocrine disruptors	Perfluorinated chemicals, polychlorinated biphenyls, dioxins, bisphenol A, perchlorate and phthalates found in foods, chemicals, and consumer products can interfere with thyroid function.
Obesity	Subclinical hypothyroidism occurs in 10%-23% of obese patients, usually as a consequence rather than a cause.
Idiopathic	Incidence unknown.
Macro-TSH	High molecular weight TSH complexes with low bioactivity. It accumulates in the circulation due to slow clearance and causes false hyperthyrotropinemia. The condition is rare (0.79% of all subclinical hypothyroidism).

PTH - parathormone; TSH - thyroid stimulating hormone.
Adapted from: Salerno M, Capalbo D, Cerbone M, De Luca F. Subclinical hypothyroidism in childhood - current knowledge and open issues. Nat Rev Endocrinol 2016;12:734-46,[3] Vigone MC, Capalbo D, Weber G, Salerno M. Mild hypothyroidism in childhood: Who, when, and how should be treated? J Endocr Soc 2018;2:1024-39,[6] and Salerno M, Improda N, Capalbo D. Management of endocrine disease: Subclinical hypothyroidism in children. Eur J Endocrinol 2020;183:R13-28.[12]

Pathophysiology

Subclinical hypothyroidism can spontaneously regress to a normal euthyroid state, subsist over time or progress to overt hypothyroidism (with low FT4). The natural history depends mainly on the associated etiology (Table 2).[13]

Thyroid stimulating hormone elevation in subclinical hypothyroidism is usually interpreted as a biochemical epiphenomenon of mild thyroid dysfunction, with reduced effects of thyroid hormones at the pituitary and peripheral tissue level.[3,7] Therefore, more marked elevations in TSH serum levels, translate to a more severe thyroid dysfunction with a higher risk of progression to overt hypothyroidism.[1,8,13]

In idiopathic subclinical hypothyroidism, spontaneous remission is usually the natural course, being a self-limited and benign condition. Indeed, in mild cases, with negative anti-peroxidase and anti-thyroglobulin antibodies (Ab), and in the absence of goiter or associated condition, a large proportion of patients (around two thirds) have normal thyroid function at the three-month follow-up. This proportion increases with a year of follow-up.[11] It is worth mentioning that worsening of thyroid function tests occurs in only 12% of cases.[6,13,14]

In the presence of chronic autoimmune thyroiditis, on the contrary, the risk of progression is higher, in about 30% to 50% of cases, with normalization in only 10%-20%,[6,7,14] although higher proportions (30%-40%) have been reported as well.[12] Risk factors for progression to overt hypothyroidism are higher TSH levels (> 7.5 mUI/L), higher antibody titers at presentation and its progressive elevation, presence of goiter, celiac disease, trisomy 21, Turner syndrome, or the presence of an associated autoimmune disease.[1,3,6] Other known risk factors include female gender and pre-pubertal state.[8,15]

Subclinical hypothyroidism is particularly common in trisomy 21 children (around 60%).[3] Beyond the neonatal period, isolated hyperthyrotropinemia can affect 85% of these infants.[16] In infants and small children, it seems to be due to hypothalamic-pituitary-thyroid axis dysregulation. It is often a transient condition that tends to normalize over time in most cases, especially in the absence of goiter or positive antibodies. On the other hand, in older children, there is a greater risk of chronic autoimmune thyroiditis, and approximately 24% of cases show deterioration or a progression to hypothyroidism.[3,16] It should be noticed that the condition in 7% of these children progresses to Graves' disease.[13,14]

In girls with Turner syndrome, the natural course is frequently more unfavorable, and common deterioration of thyroid function occurs over time (45.5% *vs* 11.9% in idiopathic cases), frequently needing treatment.[12,14]

Due to the reduced TSH cut-off in neonatal screening, potentially transient neonatal hyperthyrotropinemia has been more frequently detected. When isolated, it can be secondary to an excess or deficit of maternal or neonate iodine, drugs, and prematurity. Some genetic mutations, such as heterozygous mutations in the TSH receptor or nicotinamide adenine dinucleotide phosphate oxidase dual 2 (DUOX2), have also been associated with hyperthyrotropinemia. Slight morphological and/or thyroid gland volume changes are observed in up to 20% of cases. Information regarding the natural history is still scarce, but most cases with mild TSH elevations seem to have their function normalized over time, with about 30% experiencing persistent changes or worsening of the condition.[12]

Consequences of subclinical hypothyroidism

In addition to the risk of progression to overt hypothyroidism, the decision to treat a case of subclinical hypothyroidism is fundamentally made based on the presence of signs and symptoms and its potential long-term adverse outcomes.

Whether or not subclinical hypothyroidism causes symptoms is a matter of controversy, as the symptoms are unspecific and difficult to assess, and structural changes (goiter), clinical, and biochemical changes may be evident in some cases.[2,11]

In the adult population, the adverse effects of subclinical hypothyroidism are relatively well established, namely, insulin resistance, dyslipidemia, endothelial dysfunction, coronary heart disease, and heart failure.[3,8] In children, on the contrary, these effects are poorly understood, either due to the lack of well-designed studies or contradictory results of published studies. Also, there is no quality evidence on the potential beneficial effect of therapy in these cases.

Neurocognitive effects

Some studies suggest a subtle negative effect of subclinical hypothyroidism on attention level in older children, with no significant differences after initiation of levothyroxine treatment.[6,8] A recent study[17] demonstrated a slight compromise in cognitive skills, with prolonged latency time and evoked potentials and lower scores in visual and verbal memory that were improved after treatment. However, there are studies with contradictory results.[18,19]

Linear growth

Subclinical hypothyroidism does not appear to have any effect on final height and bone maturation,[11] even in cases with prolonged subclinical hypothyroidism.[2,3,6,8] In children with trisomy 21 and subclinical hypothyroidism (even if mild), treatment with levothyroxine in the first 3 years of life seems to have a beneficial effect on linear growth and prevent excessive weight gain.[16]

Bone homeostasis

No compromise of bone mineralization has been demonstrated.[1,3]

Obesity

Subclinical hypothyroidism is more frequent in obese patients but improves with weight loss and lifestyle changes. Therefore, it appears to be a consequence of obesity, rather than the cause.[1] There are several mechanisms proposed for hyperthyrotropinemia in obesity, including[3,20]:

- Compensatory elevation, as an adaptative mechanism to increase energy expenditure;
- A state of resistance to thyroid hormones;
- Neuroendocrine dysregulation leading to abnormal and excessive secretion of TSH.

Leptin appears to have a role affecting the hypothalamic regulation of TSH secretion. In these patients, there is often an increase in free triiodothyronine (FT3), probably adaptive and secondary to weight gain.[13,20,21] This cause-effect relationship is also notorious and opposite in *anorexia nervosa* (with a reduction in TSH and FT3 and an increase in both after weight gain).[2] Treatment with levothyroxine in obese patients with mild subclinical hypothyroidism (TSH > 5 mUI/L and < 10 mUI/L) does not seem to improve the lipid profile, weight, or body mass index, with weight loss being the most decisive factor in normalizing thyroid function and improving lipid profile,[20] although large-volume randomized trials are still needed to draw definitive conclusions.

Cardiovascular system

It is known that the atherosclerotic process begins in childhood, progresses into adulthood, and eventually leads to adverse cardiovascular events. The cardiovascular system is rich in TSH receptors and is one of the major sites of action for TSH, being relatively sensitive to variations in the TSH level.[22] Given the harmful effects of subclinical hypothyroidism in adults, a growing concern about the appearance of these effects

in children has led to several studies that demonstrate an association between subclinical hypothyroidism and early cardiovascular risk factors, such as mild dyslipidemia, increased visceral adiposity, indicators of subclinical atherosclerosis, increased homocysteine, and altered ventricular function.[2,3,7,22-24] One study revealed increased concentrations of dimethylarginine, an amino acid that is considered an early marker of endothelial dysfunction, with normalization two years after levothyroxine therapy.[3,8] In a study mild subclinical hypothyroidism was not associated with changes in body mass index, arterial pressure, and lipid and glucose metabolism after a year of follow-up without treatment, but the short follow-up time in this work could be noteworthy.[11] More recently, TSH level has been correlated with the carotid intima-media thickness, although this relationship is less expressive when considering the lipid profile.[25] This finding suggests that in obese patients, the adverse lipid profile remains the main risk factor involved. In summary, current evidence suggests that children with prolonged subclinical hypothyroidism may develop a cluster of subtle pro-atherogenic risk factors that may predispose them to cardiovascular disease in the future. There is still no conclusive evidence on the benefits of levothyroxine therapy.

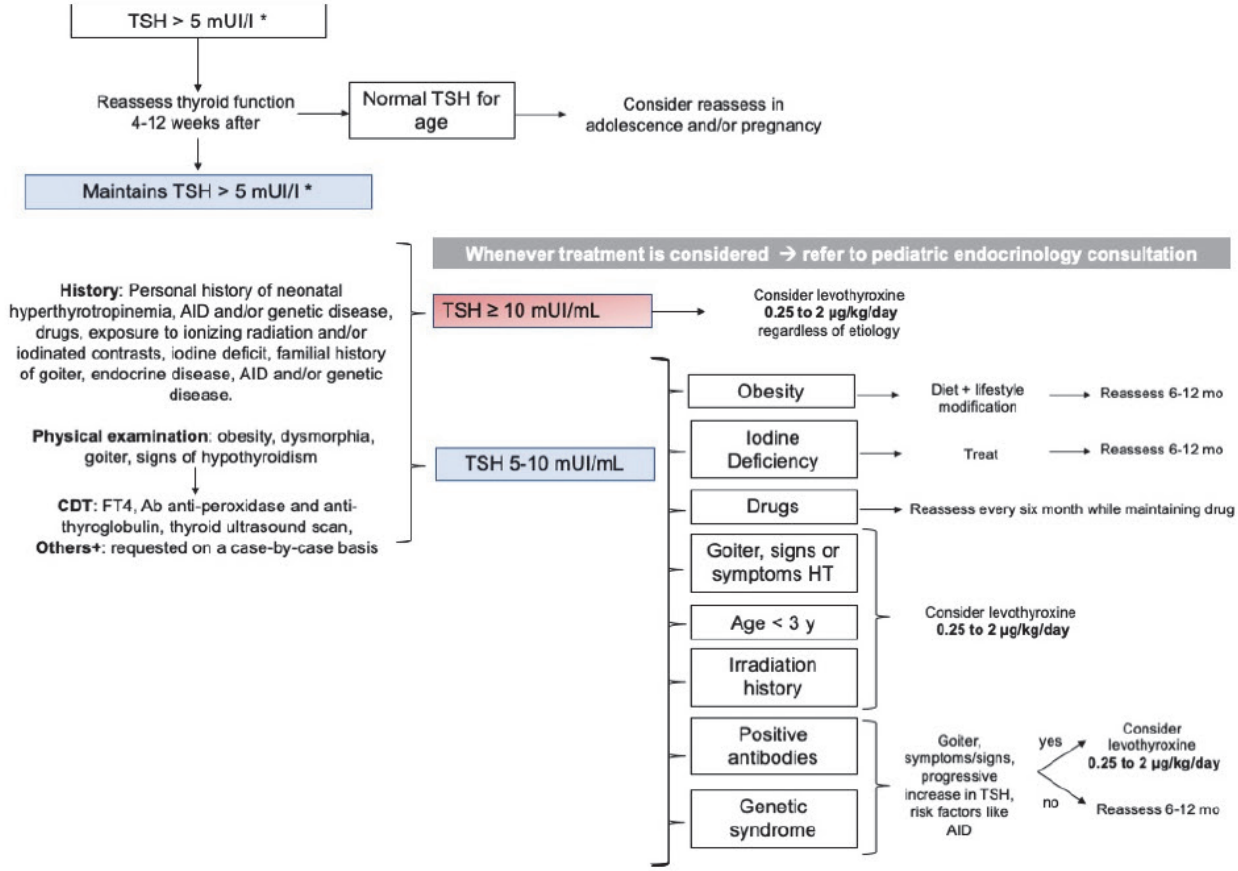
Diagnostic approach

The final algorithm is presented in Fig 1.

The first step in approaching a subclinical hypothyroidism is to exclude an abnormal value caused by laboratory error, the diurnal variation in TSH, and transient causes of elevation (recovery from an infectious complication, subacute thyroiditis) by repeating the analytical assessment four to 12 weeks later.[3,6]

In cases of persistent hyperthyrotropinemia, investigation needs to be initiated with the clinical history and physical examination, with special emphasis on:

- Personal history of neonatal hyperthyrotropinemia, autoimmune disease (*eg* celiac disease, type 1 diabetes mellitus), and/or genetic disease, such as Turner syndrome, trisomy 21, pseudohypoparathyroidism type 1A;
- Drug history;



Ab - antibodies; AID - autoimmune disease; CDT - complementary diagnostic tests; FT4 - free thyroxine HT - hypothyroidism; mo - months; TSH - thyroid stimulating hormone; y - years.
* Take into consideration the reference values according to age (Table 1).
+ Other complementary diagnostic tests to be requested on a case-by-case basis: lipid profile, glucose metabolism, parathormone, phospho-calcium metabolism; genetic study for the thyroid stimulating hormone receptor gene, Turner syndrome, pseudohypoparathyroidism type 1a.

Figure 1. Approach to subclinical hypothyroidism in children.

- Previous exposure to ionizing radiation and/or contrast products;
- Endemic iodine deficiency;
- Family history of goiter, endocrine disease, genetic or autoimmune disease;
- Physical examination and auxological assessment, with special attention to the presence of goiter, signs of hypothyroidism, and/or stigmata of genetic syndromes.

Since Hashimoto's thyroiditis is the main cause of subclinical hypothyroidism, all patients should be evaluated for the presence of antibodies (anti-peroxidase and anti-thyroglobulin) and have a thyroid ultrasound scan at baseline.[3,6]

The remaining investigation should be guided by the clinical history and diagnostic suspicion:

- Evaluation of the lipid profile and glucose metabolism in children with obesity, acanthosis, or family history of dyslipidemia and obesity.
- Screening for resistance to other hormones, namely parathormone (PTH), if clinical signs of pseudohypoparathyroidism type 1A.
- Possible genetic study for the thyroid stimulating hormone receptor gene, Turner syndrome, and pseudohypoparathyroidism type 1A.
- Urinary iodine: on an individual basis, it is of little use as it only reflects the consumption of iodine in the last few days; therefore, not routinely recommended.

Treatment

Whenever treatment is being considered, the child needs to be referred to a pediatric endocrinology consultation and treatment should be decided individually.

The decision to start treatment must be based on the analysis of the probable etiology, presence of signs and symptoms, TSH level, and associated conditions.[26] Since children who start treatment end up maintaining this therapy for a long time, the decision to treat must consider whether it could be a transitory situation or a real hypofunction.[7]

Treatment with levothyroxine (0.25-2 µg/kg/day, maximum 200 µg/day) should be considered in the following situations[1,3,6,8,15]:

- Severe subclinical hypothyroidism (TSH levels ≥ 10 mIU/L), regardless of the etiology.
- Mild subclinical hypothyroidism (TSH 5-10 mIU/L, considering the reference values for age), in patients with:
  - Age under 3 years;
  - Presence of goiter;
  - Symptoms / signs of hypothyroidism;
  - Progressive worsening during follow-up;
  - Previous irradiation history (given the trophic effect exerted by TSH on thyroid epithelial cells in post-radiation cases, subclinical hypothyroidism may increase the risk of thyroid cancer, with relevant implications for the decision to treat);
  - Conditions associated with increased risk (Turner syndrome, type 1 diabetes mellitus, celiac disease, trisomy 21).

Other treatments

- Weight loss and lifestyle changes should be promoted in children with obesity. There seems to be no benefit in starting treatment with levothyroxine, namely in terms of body mass index, adiposity, growth, and lipid profile.[21] Therefore, treatment with levothyroxine is not routinely recommended. The beneficial effects of levothyroxine in obese children and the presence of concomitant cardiovascular risk factors (*eg* dyslipidemia, family history of early cardiovascular disease, and cardiovascular dysfunction) remain open to debate.
- Iodine supplementation in deprived endemic areas.
- Stop (when possible) or replace the drug causing subclinical hypothyroidism.

Follow-up

- Clinical and thyroid function evaluation every six months (or annually in the case of mild and idiopathic TSH in children older than 3 years).
- Anti-peroxidase and anti-thyroglobulin antibodies and thyroid ultrasound every 1-2 years.
- In children with trisomy 21 or Turner syndrome, maintain regular clinical and thyroid function evaluation, at least annually, even if reverting to a euthyroid state.
- In children with subclinical hypothyroidism secondary to drugs, maintain clinical and thyroid function evaluation every six months and six months after the drug discontinuation.
- In idiopathic subclinical hypothyroidism, with mild and stable TSH elevation after two years of follow-up, assess only clinically and repeat thyroid function tests upon the appearance of goiter or symptoms / signs of hypothyroidism.
- Reassessment of thyroid function should be considered later if a child with subclinical hypothyroidism has become euthyroid, particularly in adolescence and pregnancy.

Final remarks

Although subclinical hypothyroidism is mostly a benign and self-limiting condition, the concern is whether it is a manifestation of thyroid dysfunction and whether it could have long-term effects, although mild, similar to those of clinical hypothyroidism. Currently, increasing evidence suggests an association with cardiovascular risk factors, favoring pro-atherogenic changes, although the benefit of levothyroxine treatment is still controversial. There is a relative consensus on treating severe subclinical hypothyroidism (TSH ≥ 10 mU/L), subclinical hypothyroidism associated with goiter and/or symptoms, or those that arise in some risk groups (eg type 1 diabetes mellitus, celiac disease, Turner syndrome). However, current evidence does not validate the treatment of all subclinical hypothyroidism cases, especially if mild and asymptomatic, and that the decision should be made individually, regarding the mentioned concerns.

Author Contribuitions

MAR, JSC, ALF, JF, MA, PR, RC, RAC and LS participated in the study conception or design. MAR, JSC, ALF, JF, MA, PR, RC, RAC and LS participated in acquisition of data. MAR participated in the analysis or interpretation of data. MAR participated in the drafting of the manuscript. MAR, JSC, ALF, JF, MA, PR, RC, RAC and LS participated in the critical revision of the manuscript. All authors approved the final manuscript and are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this study.

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Protection of human and animal subjects

The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki 2013).

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