



DOI: 10.4274/jcrpe.galenos.2026.2025-9-27

J Clin Res Pediatr Endocrinol 2026;18(3):498-507

Subclinical Hypothyroidism in Children: Natural History, Risk Factors, and Outcomes

✉ Nur Şeyma Zengin¹, ✉ Elif Sağsak², ✉ Seda Geylani Güleç¹

¹University of Health Sciences Türkiye, Gaziosmanpaşa Training and Research Hospital, Clinic of Pediatrics, İstanbul, Türkiye

²University of Health Sciences Türkiye, Gaziosmanpaşa Training and Research Hospital, Clinic of Pediatric Endocrinology, İstanbul, Türkiye

Cite this article as: Zengin NŞ, Sağsak E, Geylani Güleç S. Subclinical hypothyroidism in children: natural history, risk factors, and outcomes. J Clin Res Pediatr Endocrinol. 2026;18(3):498-507

ABSTRACT

Objective: Subclinical hypothyroidism (SH) is defined as elevated thyroid-stimulating hormone (TSH) with normal thyroid hormone levels and typically presents without specific symptoms in children. Although treatment criteria exist, predictors of progression and treatment need remain uncertain.

Methods: To evaluate the natural course of mild SH, identify clinical conditions associated with elevated TSH, determine predictors of progression requiring levothyroxine, and assess growth outcomes. Records of children (3 months-18 years) with mild SH (TSH 5-10 mIU/L on ≥ 2 measurements) and ≥ 6 months of follow-up were retrospectively reviewed. Demographic, biochemical, anthropometric, etiological, and imaging data were analyzed. Children were categorized as idiopathic or as having associated clinical factors (autoimmune thyroiditis, iodine imbalance, obesity, or medication use). Outcomes were classified as euthyroid, persistent SH, or requiring treatment.

Results: During follow-up, 45 of the study cohort of 111 children (40.5%) became euthyroid, 49 (44.2%) remained subclinically hypothyroid, and 17 (15.3%) required levothyroxine. Idiopathic cases showed the most favorable course, with only 8.6% requiring therapy. Hashimoto's thyroiditis (HT) was the strongest predictor of progression (42.1% vs. 9.8% in non-HT). A baseline TSH > 7.5 mIU/L increased treatment likelihood by ~ 3.5 -fold. Growth parameters remained within normal limits, with no deterioration in untreated children.

Conclusion: Mild pediatric SH is generally benign and self-limiting, particularly in idiopathic cases. HT and higher baseline TSH levels are key predictors of progression, while growth remains stable. Management should be individualized based on underlying conditions, TSH severity, and autoimmune status.

Keywords: Natural history, risk factors, subclinical hypothyroidism

What is already known on this topic?

Subclinical hypothyroidism (SH) in children is a relatively uncommon but increasingly recognized condition, with variable natural history. Most cases are idiopathic and often show spontaneous resolution or stable course without progression.

Corresponding Author: Nur Şeyma Zengin, MD., University of Health Sciences Türkiye, Gaziosmanpaşa Training and Research Hospital, Clinic of Pediatrics, İstanbul, Türkiye

E-mail: nszengin37@hotmail.com **ORCID:** orcid.org/0000-0001-7926-0064

Conflict of interest: None declared

Received: 30.09.2025 **Accepted:** 04.03.2026 **Epub:** 31.03.2026 **Publication Date:** 08.09.2026



©Copyright 2026 by Turkish Society for Pediatric Endocrinology and Diabetes / The Journal of Clinical Research in Pediatric Endocrinology published by Galenos Publishing House. Licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 (CC BY-NC-ND) International License.

What this study adds?

This study describes one of the largest pediatric cohorts with mild SH from Türkiye, demonstrating its predominantly benign course. Higher baseline thyroid-stimulating hormone levels and Hashimoto's thyroiditis emerged as key factors associated with progression. Stable growth parameters across follow-up support existing evidence that untreated mild SH does not adversely affect growth.

Introduction

Subclinical hypothyroidism (SH) is defined by elevated serum thyroid-stimulating hormone (TSH) with normal thyroid hormone (tri-iodothyronine and thyroxine) levels and the absence of specific clinical signs (1,2). The normal range of TSH (approximately 0.4-0.5 to 4.0-5.0 μ U/mL) varies across assays, and mild SH, typically defined as TSH 4.5-10 mIU/L, encompasses most pediatric cases (3,4). Several descriptive terms are used in clinical practice to characterize mild TSH elevation. "Isolated hyperthyrotropinemia" refers to mild or transient increases in TSH levels without evidence of intrinsic thyroid dysfunction, whereas "primary compensated hypothyroidism" denotes early thyroid impairment that warrants closer clinical observation. Importantly, mild TSH elevation does not always indicate true thyroid disease; transient increases associated with obesity, fluctuations in iodine intake, or recovery from non-thyroidal illness may represent adaptive physiological responses rather than pathological conditions (5).

In children, SH arises in a wide range of clinical contexts, including autoimmune thyroiditis, iodine imbalance, congenital thyroid anomalies, genetic syndromes, medication effects, and idiopathic presentations (6,7). Idiopathic SH is characterized by mildly elevated TSH levels despite normal peripheral thyroid hormones and the absence of autoimmunity or identifiable secondary contributors (3). Most children are asymptomatic, and occasional nonspecific symptoms, such as dry skin, fatigue, or weight gain, are not diagnostic (8,9,10).

The natural history of SH differs between children and adults. Pediatric SH often remains stable or normalizes spontaneously, and progression to overt hypothyroidism (OH) occurs in a minority of cases (0-28%) (11,12,13).

Children with SH due to HT have a higher risk of deterioration (14,15), a risk that may further increase in chromosomal disorders such as Turner or Down syndrome (13). Among clinical and biochemical variables, baseline TSH is considered the strongest predictor of outcome (16).

Although OH impairs growth and neurocognitive development, the significance of untreated mild SH remains uncertain. Most evidence indicates no adverse effects on growth, bone maturation, or cognition, though subtle metabolic changes have been described (2,4).

Current recommendations favor observation in asymptomatic, antibody-negative children with TSH<10 mIU/L, and treatment in those with symptoms, goiter, autoimmunity, or rising TSH (4,10,17,18).

Given these considerations, the aim of the present study was to characterize the natural course of mild SH in a Turkish cohort, identify clinical conditions that accompany TSH elevation and may provide a background for SH, determine predictors of progression requiring treatment, and evaluate growth outcomes in affected children.

Methods

Study Design and Population

This single-center retrospective study included children aged 3 months to 18 years who presented to the Pediatric Endocrinology Outpatient Clinic of University of Health Sciences Türkiye, Gaziosmanpaşa Training and Research Hospital between 2016 and 2019.

Mild SH was defined as two TSH measurements of 5-10 mIU/L obtained ≥ 4 weeks apart, with normal free thyroxine (fT4) levels. Since SH is a biochemical state, conditions potentially influencing TSH, including obesity, genetic syndromes, medication use, and prior chemotherapy/radiotherapy, were not exclusion criteria. Patients with TSH>10 mIU/L, abnormal fT4, or known thyroid disease requiring treatment were excluded.

Study Procedure

The following variables were collected: date of admission, sex, presenting symptoms, age, history of regular medication use, comorbidities, use of iodized salt, family history of thyroid disease, height, body weight, physical examination findings, TSH, fT4, free triiodothyronine (fT3), anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-Tg) autoantibody status, urinary iodine concentration, and thyroid ultrasonography (USG) results. These variables were used to evaluate potential factors associated with mild SH, risk factors for requiring treatment, growth outcomes, and indications for therapy.

The etiological classification was made based on potential contributing factors described in the pediatric endocrinology literature; no causality was inferred. Conditions such as autoimmune thyroiditis, obesity, genetic syndromes, iodine deficiency, congenital thyroid malformations, medications

affecting thyroid function, and history of radiotherapy or chemotherapy were investigated.

For growth evaluation, height, weight, body mass index (BMI), and growth velocity were expressed as standard deviation scores (SDS) using the reference data of Neyzi et al. (19). Growth velocity SDS was calculated using the charts of Neyzi et al. (19) for girls aged 8-13 years and boys aged 10-15 years, and Baumgartner et al.'s (20) data for younger ages. Growth velocity could not be assessed in 37 patients due to levothyroxine initiation, epiphyseal closure, growth-affecting medications, Down syndrome, or prior chemotherapy.

Serum TSH, fT4, and fT3 were measured with immunoenzymatic assays on DXI 800 analyzers (Beckman Coulter Biyomedikal Ürünler San. ve Tic. Ltd. Şti., İçerenköy, İstanbul, Türkiye). Anti-TPO >9 IU/mL and anti-Tg >4 IU/mL were considered positive.

Urinary Iodine Concentration (UIC) was analyzed externally (Düzen Laboratory, Türkiye) using an ICP-MS system. Reference intervals were based on the World Health Organization (WHO) 2007 guideline, originally expressed in µg/L (21). After unit conversion, these correspond to the standard µg/L categories. UIC levels were therefore classified according to WHO 2007 interpretive criteria (21): <20 µg/L severe; 20-49 µg/L moderate; 50-99 µg/L mild; 100-199 µg/L adequate; 200-299 µg/L above requirements; and ≥300 µg/L excessive iodine levels.

Patient Follow-up and Treatment

After the diagnosis of SH (defined as elevated TSH and normal fT4 levels on at least two separate measurements) was confirmed, the date of diagnosis was designated as "Day 0." Following this, risk factors associated with the need for treatment, including autoimmune thyroiditis, goiter, higher baseline TSH levels, obesity, and chromosomal or autoimmune comorbidities, such as Down or Turner syndrome, were evaluated. In patients with goiter or strong risk indicators, thyroid USG was performed to assess gland size and echogenic heterogeneity suggestive of autoimmune thyroiditis.

In routine practice, patients without risk factors were advised to undergo clinical evaluation and TSH/fT4 measurement every 3-6 months, whereas those with goiter, autoimmune thyroiditis, higher baseline TSH levels (> 7.5-10 mIU/L), or other high-risk features were scheduled for re-evaluation within 1-3 months. However, due to the retrospective design of the study, variable appointment adherence, and differences in healthcare accessibility, follow-up intervals varied among patients. Therefore, only the initial (diagnostic) and the last available follow-up visits were included in the analysis, and patients with a follow-up duration of less than six months were excluded. The decision to initiate levothyroxine therapy was based on

predefined biochemical and clinical indicators consistent with standard clinical practice. Specifically, TSH levels >10 mIU/L, a decline or downward trend in fT4, the presence of goiter, or clinical signs suggestive of OH were accepted as primary criteria for treatment initiation.

Ethical Considerations

This study was conducted as a specialty thesis in the Clinic of Pediatrics, University of Health Sciences Türkiye, Gaziosmanpaşa Training and Research Hospital. The study was carried out in accordance with the principles of the Declaration of Helsinki and was approved by the Clinical Research Ethics Committee of University of Health Sciences Türkiye, Taksim Training and Research Hospital (approval no: 102, date: 24.07.2019). Due to the retrospective design of the study, informed consent was not required.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics for Windows, Version 27.0 (IBM Corp., Armonk, NY, USA). The distribution of continuous variables was assessed using the Shapiro-Wilk test. Descriptive statistics (mean, standard deviation, frequency) were calculated. Group comparisons for normally distributed variables were performed using the Student's t-test for two groups and one-way ANOVA for more than two groups, while differences between baseline and follow-up values were evaluated with the paired-samples t-test. Correlations between normally distributed parameters were assessed using Pearson correlation coefficients. The mean growth velocity SDS was compared with population reference values for healthy children using the one-sample t-test. Categorical variables were analyzed using the Pearson chi-square test or Fisher's exact test, and the Fisher-Freeman-Halton test was applied for larger contingency tables. The linear-by-linear association test was used to assess trends across ordered categories. To estimate the association between baseline TSH levels and treatment requirement, the odds ratio with 95% confidence interval (95% CI) was calculated. A p-value <0.05 was considered statistically significant.

Results

General Characteristics of the Patients

Among 175 patients initially identified with mildly elevated TSH, 111 were eligible after excluding those with follow-up <6 months or who were lost to follow-up. None had received thyroid-related treatment at admission. General characteristics of the 111 children with mild SH are shown in Table 1. A family history of thyroid disease was present in 49 patients (44.1%), most commonly thyroid nodules (46.9%), goiter (20.4%), autoimmune thyroiditis (12.2%), hypothyroidism (8.2%), thyroid cancer (2.0%), and unspecified thyroid disorders (10.2%).

Overall Follow-up Outcomes

During follow-up, 45 children (40.5%) became euthyroid, 49 (44.2%) remained subclinically hypothyroid, and 17 (15.3%) required levothyroxine. Of those requiring treatment, 10 (58.8%) were female and seven (41.2%) were male.

Treatment indications were isolated TSH>10 mIU/L (n=7; 41.2%), low fT4 (n=3; 17.6%), newly developed goiter (n=3; 17.6%), goiter accompanied by TSH>10 mIU/L (n=1; 5.9%), short stature (n=2; 11.8%), and weight loss with poor appetite (n=1; 5.9%) (Figure 1). Among treated children, one had valproic acid use (TSH>10 mIU/L) and one had prior chemotherapy/radiotherapy (low fT4).

Table 1. General characteristics of the patients

Variable	Mean±SD	Min-Max	n	%
Age (years)			111	
First visit	8.28±4.39	0.37-17.0		
Last visit	9.14±4.47	1.0-17.6		
Follow-up duration (years)	0.86±0.53	0.5-3.0	111	
Gender			111	
Female			59	53.2
Male			52	46.8
Family history of thyroid disease			111	
Absent			62	55.9
Present			49	44.1
Body weight SDS			111	
First visit	-0.06±1.31	-3.50-2.96		
Last visit	-0.09±1.34	-4.19-2.72		
Height SDS			111	
First visit	-0.46±1.28	-4.47-2.36		
Last visit	-0.45±1.31	-4.45-3.02		
BMI SDS			111	
First visit	0.24±1.18	-2.09-3.07		
Last visit	0.17±1.20	-2.09-3.11		
Growth velocity SDS	0.21±1.32	-3.38-4.27	74	
Growth velocity was evaluated in 74 untreated children after excluding those with factors that could affect growth (e.g., epiphyseal closure, growth-suppressing medications, Down syndrome, prior chemotherapy)				
BMI: body mass index; SD: standard deviation, SDS: standard deviation score, n: number of patients				

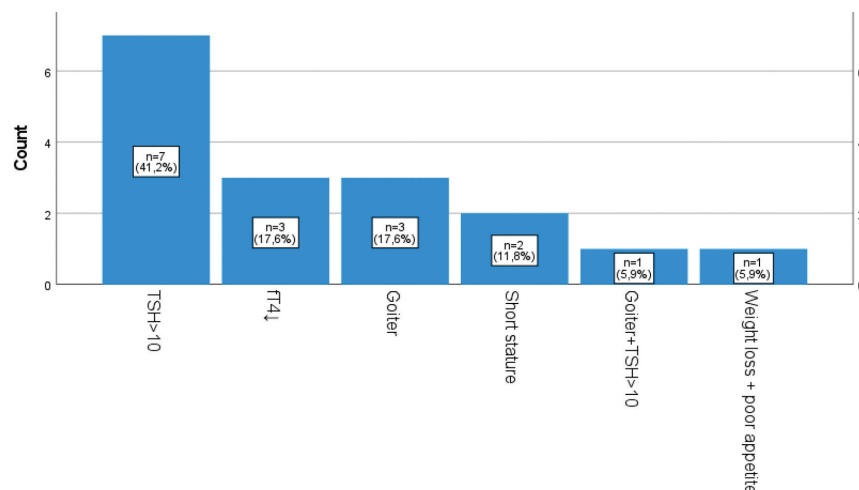


Figure 1. Reasons for initiation of treatment in the study cohort

Overall, 58.8% were treated due to biochemical deterioration, 35.3% due to clinical or structural findings, and 5.9% due to combined abnormalities.

Children requiring treatment had higher baseline TSH levels ($p=0.012$). Baseline TSH levels differed significantly among follow-up outcome groups (Kruskal-Wallis test, $p=0.018$), with post-hoc analyses demonstrating that this difference was primarily driven by higher baseline TSH levels in children who required treatment compared with those who became euthyroid (adjusted $p=0.020$). Although children requiring treatment tended to be older at diagnosis ($p=0.049$), post-hoc analyses did not confirm a statistically significant age difference between groups. Sex distribution, family history, BMI SDS, and UIC status did not differ significantly. Detailed baseline comparisons according to follow-up outcomes are provided in Table 2.

Potential Factors Contributing to the Etiology of SH

Among the 111 children with SH, no specific etiological factor was identified in 70 patients (63%). Factors contributing to the etiology included autoimmune thyroiditis (HT; $n=19$, 17.1%), low UIC ($n=10$; 9%), obesity ($n=9$; 8.1%), valproic acid use ($n=5$;

4.5%), and Down syndrome ($n=4$; 3.6%). In addition, one patient (0.9%) had a history of radiotherapy/chemotherapy, and one (0.9%) had congenital agenesis of the right thyroid lobe. Several children had overlapping factors, including HT with iodine deficiency ($n=2$), HT with valproic acid therapy ($n=1$), HT with obesity ($n=3$), and Down syndrome with valproic acid therapy ($n=1$). Therefore, the total number of etiology-contributing factors ($n=119$) exceeded the number of patients.

Comparison According to the Presence of Hashimoto's Thyroiditis

A total of 19 patients (17.1%) had HT, while 92 (82.9%) had no autoimmunity. Patients with HT were older at both baseline and final visits ($p<0.001$ for both), and female predominance was more pronounced (78.9% vs. 52.2%, $p=0.013$). Baseline TSH and follow-up duration were similar between groups ($p=0.681$ and $p=0.853$, respectively).

At follow-up, euthyroidism was achieved in 26.3% of HT patients and 43.5% of non-HT patients ($p=0.048$), while persistence of SH was comparable (31.6% vs. 46.7%, $p=0.484$). Levothyroxine therapy was required significantly more often in the HT group (42.1% vs. 9.8%, $p=0.005$) (Table 3). Consistently, HT was more

Table 2. Comparison of demographic and clinical characteristics between outcome groups

Variable	Normalized n=45 (%)	Stable n=49 (%)	Progressed n=17 (%)	p-value
Sex★				0.725
Female	31 (68.9%)	36 (73.5%)	12 (70.6%)	-
Male	14 (31.1%)	13 (26.5%)	5 (29.4%)	-
Age at diagnosis (years)	7.9±3.9	7.8±4.6	10.7±4.5	0.049
Follow-up duration (years)	0.89±0.42	0.79±0.54	0.99±0.76	0.365
Baseline TSH (mIU/L)	6.64±1.09	7.15±1.36	7.67±1.27	0.012
Baseline fT4 (ng/dL)	0.91±0.18	0.86±0.13	0.80±0.12	0.058
Family history of thyroid disease★	24 (53.3%)	17 (34.7%)	11 (64.7%)	0.090
Hashimoto thyroiditis†	5 (11.1%)	6 (12.2%)	8 (47.1%)	0.005
Idiopathic etiology†	32 (71.1%)	32 (65.3%)	6 (35.3%)	0.030
Use of medications affecting thyroid function (VPA etc.) †	2 (4.4%)	2 (4.1%)	1 (5.9%)	1.000
Obesity†	2 (4.4%)	4 (8.2%)	3 (17.6%)	0.236
BMI SDS	0.24±1.07	0.08±1.27	0.26±1.33	0.766
Urinary iodine status (n=39)†	Normalized n=16 (%)	Stable n=19 (%)	Progressed n=4 (%)	0.823
Severe deficiency	0 (0%)	1 (5.3%)	0 (0%)	
Moderate deficiency	0 (0%)	1 (5.3%)	0 (0%)	
Mild deficiency	4 (25.0%)	2 (10.5%)	2 (50.0%)	
Optimal	8 (50.0%)	8 (42.1%)	2 (50.0%)	
Above requirement	2 (12.5%)	3 (15.8%)	0 (0%)	
Excessive	2 (12.5%)	4 (21.1%)	0 (0%)	

Continuous variables were analyzed using one-way ANOVA with Tukey HSD post-hoc test. Categorical variables were analyzed using Pearson's chi-square (★) or Fisher's exact test (†), depending on expected cell counts. Statistical significance was set at $p<0.05$. Bold values indicate significance

SH: subclinical hypothyroidism, TSH: thyroid-stimulating hormone, fT4: free thyroxine, BMI: body mass index, SDS: standard deviation score, VPA: valproic acid

frequent in the treatment group (47.1%) than in the euthyroid (11.1%) or persistent SH groups (12.2%) ($p=0.005$) (Table 2).

Among treated patients, indications differed by HT status. In the HT group ($n=8$), treatment was initiated for goiter ($n=3$), TSH >10 mIU/L ($n=2$), low fT4 ($n=2$), or combined goiter + elevated TSH ($n=1$). In the non-HT group ($n=9$), indications included TSH >10 mIU/L ($n=5$), low fT4 ($n=1$), short stature ($n=2$), and weight loss with poor appetite ($n=1$) (Table 3).

To isolate autoimmune effects, patients with HT plus additional etiological factors were excluded. Among isolated HT cases ($n=13$), 30.8% became euthyroid, 38.5% remained SH, and 30.8% required treatment. In idiopathic SH ($n=70$), these rates were 45.7%, 45.7%, and 8.6%, respectively ($p=0.075$).

Urinary Iodine Status

Urinary iodine was measured in 39 patients. The findings were: severe deficiency in one (2.6%), moderate in one (2.6%), mild in eight (20.5%), optimal levels in 18 (46.2%), levels indicating risk for iodine-induced hyperthyroidism in five (12.8%), and other adverse outcomes in six (15.4%) (Table 2).

Baseline TSH and Treatment Requirement

When patients were categorized by baseline TSH level, those with TSH >7.5 mIU/L had a significantly higher likelihood of requiring levothyroxine therapy compared with those whose baseline TSH was ≤ 7.5 mIU/L (27.0% vs. 9.5%). This association remained significant in both Pearson's chi-square ($p=0.015$) and Fisher's exact test ($p=0.024$), and was further supported by the likelihood ratio test ($p=0.019$) and a significant linear-by-linear trend ($p=0.016$). Children with baseline TSH >7.5 mIU/L had approximately 3.5-fold higher odds of treatment initiation (odds ratio=3.55; 95% CI: 1.22-10.28) (Table 4).

Table 3. Comparison of HT and non-HT SH groups

Variable	HT group n=19	Non-HT group n=92	p-value
Age at first visit (years)★	11.5±3.5	7.6±4.3	<0.001
Age at last visit (years)★	12.4±3.7	8.5±4.3	<0.001
Female, n (%)†	15 (78.9%)	48 (52.2%)	0.013
Baseline TSH (mIU/L)★	7.14±1.27	7.00±1.29	0.681
Follow-up duration (years)★	0.88±0.60	0.85±0.52	0.853
Became euthyroid†	5 (26.3%)	40 (43.5%)	0.048
Persistent SH†	6 (31.6%)	43 (46.7%)	0.484
Required levothyroxine†	8 (42.1%)	9 (9.8%)	0.005
Main reasons for treatment	n=8 (%)	n=9 (%)	
TSH >10 mIU/L	2 (25.0%)	5 (55.6%)	-
Low fT4	2 (25.0%)	1 (11.1%)	-
Short stature	-	2 (22.2%)	-
Weight loss / poor appetite	-	1 (11.1%)	-
Goiter	3 (37.5%)	-	-
Goiter + TSH >10	1 (12.5%)	-	-

Continuous variables were analyzed using the Independent Samples t-test, categorical variables were analyzed using Pearson's chi-square test or Fisher's exact test when appropriate, $p<0.05$ was considered statistically significant
 ★: Independent-samples t-test; †: Pearson's chi-square test or Fisher's exact test, as appropriate
 HT: Hashimoto's thyroiditis, SH: subclinical hypothyroidism, TSH: thyroid-stimulating hormone, fT4: free thyroxine, BMI: body mass index, SDS: standard deviation score

Table 4. Treatment requirement according to baseline TSH categories

Variable	TSH ≤ 7.5 mIU/L n=74 (%)	TSH >7.5 mIU/L n=37 (%)	Total n=111 (%)	p/OR
No treatment, n (%)	67 (90.5%)	27 (73.0%)	94 (84.7%)	-
Treatment initiated, n (%)	7 (9.5%)	10 (27.0%)	17 (15.3%)	0.015 ¹ /0.024 ² OR=3.55 (1.22-10.28)
Total, n (%)	74 (66.7%)	37 (33.3%)	111 (100%)	-

¹Pearson's chi-square test, ²Fisher's exact test (used due to small expected cell counts). Likelihood ratio and linear-by-linear association tests also supported the results. Odds ratio (OR) with 95% confidence interval (CI) was reported. $p<0.05$ was considered statistically significant
 TSH: thyroid-stimulating hormone

Changes in Thyroid Hormone Levels

In the whole cohort (n=111), TSH levels declined significantly from baseline to the final visit (p<0.001), while fT4 levels remained stable (p=0.605).

TSH Changes by BMI-SDS Classification

Of the 111 children, 8.1% were obese (n=9), 18.9% overweight (n=21), 71.2% normal weight (n=79), and 1.8% underweight (n=2). Baseline TSH did not differ between groups (p=0.614).

At the final visit, TSH differed significantly between BMI categories (p=0.012). Obese children had higher final TSH than normal-weight (p=0.036) and overweight peers (p=0.007). No difference was found between normal-weight and overweight groups (p=0.479).

During follow-up, TSH decreased significantly in normal-weight and overweight groups (both p<0.001), but not in obese (p=0.648) or underweight children (p=0.727) (Table 5). TSH normalization was more frequent in non-obese children.

Clinical Outcomes by BMI-SDS

In the outcome evaluation according to BMI-SDS groups, progression requiring levothyroxine therapy was observed in 12 of 79 normal-weight children (15.2%), 2 of 21 overweight children (9.5%), and 3 of 9 obese children (33.3%). However, the difference between groups was not statistically significant (p=0.282).

Growth Outcomes

No significant changes in weight SDS, height SDS, or BMI SDS were observed between baseline and follow-up (all p>0.05). Among untreated children (n=94), baseline and final anthropometric values were also similar.

Growth velocity in untreated patients (n=74) remained normal (mean SDS=0.21±1.32; median=0.16; p=0.172).

Discussion

The present study contributes to the limited evidence on the natural course and determinants of SH in childhood. Previous studies have reported a pediatric SH prevalence ranging from

1% to 9.5% (3,22,23). The widespread use of thyroid testing in routine pediatric care has increased incidental detections, creating uncertainty about which children require treatment and which can be safely monitored.

In this cohort, most children with mild SH either normalized or maintained stable thyroid function during follow-up. Only 15.3% eventually required levothyroxine therapy. When the analysis was restricted to the idiopathic subgroup, the treatment requirement decreased to 8.6%. This supports the suggestion that SH without identifiable pathology usually follows a benign course (22,24).

These observations agree with the findings of De Luca et al. (25), who showed decreasing TSH levels, stable fT4 levels, and no adverse clinical outcomes in children with idiopathic SH followed for two years. Taken together, these results support a conservative management approach, unless biochemical or clinical deterioration occurs.

In the present study, levothyroxine was initiated for markedly elevated TSH, low fT4, the development of goiter, or other clinically relevant findings, including short stature or weight loss with poor appetite, when judged to be potentially related to thyroid dysfunction. Only 11 of 111 children (9.9%) required treatment solely due to biochemical deterioration, which aligns with reports indicating that mild pediatric SH rarely requires therapy in the absence of autoimmunity or structural abnormalities (26). In the literature, the proportion of children with mild SH requiring medical treatment has been reported to range between approximately 2% and 12% (22,27). Our findings indicated that the natural course of SH varied according to the underlying etiology, although this suggestion requires additional data to validate it.

The etiological background of SH in childhood is diverse. In our cohort, no specific etiology was identified in 63 percent of patients, consistent with previous reports in which idiopathic cases constitute the majority (28). In the remaining patients, factors thought to predispose to SH included HT, iodine imbalance, obesity, and medication-related effects.

Table 5. Evaluation of baseline and final TSH means according to BMI groups					
Variable	Underweight n=2 (1.8%)	Normal n=79 (71.2%)	Overweight n=21 (18.9%)	Obese n=9 (8.1%)	p ¹
Baseline TSH (mIU/L)	6.02±1.06	7.09±1.31	6.85±1.11	7.10±1.45	0.614
Final TSH (mIU/L)	6.70±1.03	5.48±2.17	4.66±2.04	7.70±3.91	0.012
p ² (Paired t-test)	0.727	<0.001	<0.001	0.648	-
¹ One-way ANOVA (post-hoc: Tukey HSD), ² Paired Samples t-test Levene's test confirmed homogeneity of variances (p=0.353) Bold values indicate statistical significance (p<0.05) BMI: body mass index;TSH: thyroid-stimulating hormone;SDS: standard deviation score, CI: confidence interval					

HT was the most common identifiable cause in our cohort (17.1%). It predominantly affected older and female patients, consistent with reported epidemiology (29,30,31). The clinical course was less favorable in children with HT. Treatment was required in 42.1% of children with HT compared with 9.8% of those without autoimmunity. Even when the comparison was restricted to isolated HT and idiopathic SH, progression remained more frequent in the HT group (30.8% vs. 8.6%). These findings align with multicenter studies reporting a higher risk of progression when SH coexists with thyroid autoimmunity (13,32,33,34). In HT positive children, goiter or biochemical decline were major determinants of treatment. In idiopathic SH, treatment was mainly initiated for rising TSH or growth related concerns. This pattern suggests that idiopathic SH generally follows a stable course, whereas in HT-positive children treatment decisions were more often driven by objective findings, such as goiter or biochemical deterioration.

Iodine status is an important component of thyroid physiology (35,36,37,38). Although some population studies have described a U shaped association between UIC and TSH (39), a recent meta analysis found inconsistent relationships in the mild to moderate deficiency range (40). In our cohort, severe iodine deficiency was uncommon, whereas mild to moderate deficiency was more frequent. However, as UIC was measured only once and in a relatively limited subset of patients, these findings should be interpreted with caution, as single measurements may reflect short-term dietary fluctuations rather than true, persistent deficiency. All children with iodine deficiency were advised to use iodized salt but only one patient with documented deficiency reported not consuming iodized salt. As UIC was not reassessed during follow-up, the effect of iodine supplementation on subsequent TSH trajectories could not be evaluated, representing an inherent limitation of the retrospective study design.

Obesity has been associated with higher TSH levels in numerous pediatric studies. The prevalence of SH ranges between 7-23% in obese children, whereas it remains around 2% in their normal-weight peers (41,42), and national data from the KNHANES VI similarly reported SH rates of 24.3% in obese and 12.8% in non-obese children (43). In our cohort, 27.9% of children were overweight or obese, which is consistent with previous reports (27,44). Although the mechanism underlying elevated TSH in obesity is not fully understood, increased leptin is known to stimulate Thyrotropin Releasing Hormone (TRH) and TSH secretion, while weight loss reduces both leptin and TSH levels (45,46). In our cohort, baseline TSH levels did not differ significantly across BMI groups; however, during follow-up, TSH elevation persisted in obese children, whereas significant declines were observed in normal-weight and overweight peers. Although treatment was required more frequently in obese children, this was not significant. These findings suggest that TSH

elevation in obesity may reflect not only an adaptive response but, in some cases, early alterations in the hypothalamic-pituitary-thyroid axis (46,47,48,49).

The magnitude of TSH elevation at diagnosis serves as a surrogate for the intrinsic functional reserve of the thyroid axis. Although pediatric SH generally follows a benign and often reversible course, our findings show that children with baseline TSH greater than 7.5 mIU/L constitute a subgroup with a higher likelihood of deterioration. Recognizing this threshold may assist clinicians in identifying patients who require closer follow-up and earlier therapeutic consideration.

Growth and bone development were not adversely affected in our cohort, consistent with several previous studies. Longitudinal studies in untreated children with SH have similarly reported no significant changes in height SDS, BMI SDS, or growth velocity compared with healthy controls, suggesting that mild thyroid dysfunction does not interfere with growth regulation (12,24,27,50). In our cohort, mean growth velocity SDS was 0.21 ± 1.32 , which was comparable to the population mean, further supporting the suggestion that mild SH is unlikely to impair somatic growth or bone maturation in the short to medium term.

Overall, our findings support the growing body of evidence that idiopathic pediatric SH is often a benign and self-limiting condition, whereas SH associated with HT carries a higher likelihood of requiring treatment. Baseline TSH > 7.5 mIU/L also appeared to be a predictive factor in our cohort. Management decisions should be individualized, taking into account the underlying etiology, the severity of biochemical abnormalities, and the presence of clinical features.

Study Limitations

This study has several limitations. First, its retrospective design resulted in heterogeneous follow-up intervals and variable follow-up durations, which may have influenced the estimation of progression or regression rates. Second, the overall follow-up period was relatively short, limiting the ability to fully characterize the long-term natural course of mild SH and its potential effects on growth. Future prospective studies with standardized and extended follow-up schedules are warranted.

A small number of patients presented with clinical factors known to influence TSH levels, such as genetic syndromes, use of medications affecting thyroid function, or a history of chemotherapy/radiotherapy. These cases were intentionally included to reflect real-world clinical practice. However, they may introduce potential confounding and should be considered when interpreting the results.

Finally, although predefined index and final visits were used to minimize bias arising from irregular appointment intervals, this approach while improving generalizability, limited the evaluation of time-dependent trends in thyroid function.

Conclusion

In this Turkish cohort, mild SH in children demonstrated a predominantly benign and stable course. Idiopathic cases showed the most favorable outcomes, whereas HT and higher baseline TSH levels were the main predictors of progression requiring treatment. Although TSH elevations tended to persist in obese children, no adverse effects on growth were observed. These findings support an individualized follow-up strategy based on underlying clinical conditions, baseline TSH severity, and autoimmune status. Larger prospective studies are needed to refine risk-based monitoring and management approaches.

Ethics

Ethics Committee Approval: The study was carried out in accordance with the principles of the Declaration of Helsinki and was approved by the Clinical Research Ethics Committee of University of Health Sciences Türkiye, Taksim Training and Research Hospital (approval no: 102, date: 24.07.2019).

Informed Consent: Due to the retrospective design of the study, informed consent was not required.

Acknowledgements

This article is derived from the medical specialty thesis of Dr. Nur Şeyma Zengin, completed at the Clinic of Pediatrics, University of Health Sciences Türkiye, Gaziosmanpaşa Training and Research Hospital, İstanbul, Türkiye (2020).

Footnotes

Authorship Contributions

Surgical and Medical Practices: Nur Şeyma Zengin, Elif Sağsak, Concept: Nur Şeyma Zengin, Elif Sağsak, Seda Geylani Güleç, Design: Nur Şeyma Zengin, Elif Sağsak, Seda Geylani Güleç, Data Collection or Processing: Nur Şeyma Zengin, Elif Sağsak, Analysis or Interpretation: Nur Şeyma Zengin, Literature Search: Nur Şeyma Zengin, Writing: Nur Şeyma Zengin.

Financial Disclosure: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, Franklyn JA, Hershman JM, Burman KD, Denke MA, Gorman C, Cooper RS, Weissman NJ. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. *JAMA*. 2004;291:228-238.
2. Vigone MC, Capalbo D, Weber G, Salerno M. Mild hypothyroidism in childhood: who, when, and how should be treated? *J Endocr Soc*. 2018;2:1024-1039.
3. Murillo-Vallés M, Martínez S, Aguilar-Riera C, García-Martin MA, Bel-Comós J, Ybern MLG. Subclinical hypothyroidism in childhood, treatment or only follow-up? *BMC Pediatr*. 2020;20:282.
4. Salerno M, Capalbo D, Cerbone M, De Luca F. Subclinical hypothyroidism in childhood - current knowledge and open issues. *Nat Rev Endocrinol*. 2016;12:734-746. Epub 2016 Jul 1
5. Van Vliet G, Deladoëy J. Interpreting minor variations in thyroid function or echostructure: treating patients, not numbers or images. *Pediatr Clin North Am*. 2015;62:929-942. Epub 2015 Jun 24
6. Salerno M, Improda N, Capalbo D. Management of endocrine disease: subclinical hypothyroidism in children. *Eur J Endocrinol*. 2020;183:R13-R28.
7. Metwalley KA, Farghaly HS. Subclinical hypothyroidism in children: updates for pediatricians. *Ann Pediatr Endocrinol Metab*. 2021;26:80-85. Epub 2021 Jun 30
8. Yürekli BŞ, Kabalak T, Altiner S. The issue of subclinical hypothyroidism: should it be treated or not? *Türkiye Klin J Endocrin*. 2016;11:55-64.
9. Biondi B, Fazio S, Palmieri EA, Carella C, Panza N, Cittadini A, Bonè F, Lombardi G, Saccà L. Left ventricular diastolic dysfunction in patients with subclinical hypothyroidism. *J Clin Endocrinol Metab*. 1999;84:2064-2067.
10. Bona G, Prodam F, Monzani A. Subclinical hypothyroidism in children: natural history and when to treat. *J Clin Res Pediatr Endocrinol*. 2013;5(Suppl 1):23-28. Epub 2012 Nov 15
11. Gao N, Zhang W, Zhang YZ, Yang Q, Chen SH. Carotid intima-media thickness in patients with subclinical hypothyroidism: a meta-analysis. *Atherosclerosis*. 2013;227:18-25. Epub 2012 Nov 6
12. Cerbone M, Bravaccio C, Capalbo D, Polizzi M, Wasniewska M, Cioffi D, Improda N, Valenzise M, Bruzzese D, De Luca F, Salerno M. Linear growth and intellectual outcome in children with long-term idiopathic subclinical hypothyroidism. *Eur J Endocrinol*. 2011;164:591-597. Epub 2011 Feb 3
13. Wasniewska M, Aversa T, Salerno M, Corrias A, Messina MF, Mussa A, Capalbo D, De Luca F, Valenzise M. Five-year prospective evaluation of thyroid function in girls with subclinical mild hypothyroidism of different etiology. *Eur J Endocrinol*. 2015;173:801-808. Epub 2015 Sep 15
14. Aversa T, Corrias A, Salerno M, Tessaris D, Di Mase R, Valenzise M, Corica D, De Luca F, Wasniewska M. Five-year prospective evaluation of thyroid function test evolution in children with Hashimoto's thyroiditis presenting with either euthyroidism or subclinical hypothyroidism. *Thyroid*. 2016;26:1450-1456. Epub 2016 Sep 13
15. Rodondi N, den Elzen WP, Bauer DC, Cappola AR, Razvi S, Walsh JP, Asvold BO, Iervasi G, Imaizumi M, Collet TH, Bremner A, Maisonneuve P, Sgarbi JA, Khaw KT, Vanderpump MP, Newman AB, Cornuz J, Franklyn JA, Westendorp RG, Vittinghoff E, Gussekloo J; Thyroid Studies Collaboration. Subclinical hypothyroidism and the risk of coronary heart disease and mortality. *JAMA*. 2010;304:1365-1374.
16. Wasniewska M, Corrias A, Aversa T, Valenzise M, Mussa A, De Martino L, Lombardo F, De Luca F, Salerno M. Comparative evaluation of therapy with L-thyroxine versus no treatment in children with idiopathic and mild subclinical hypothyroidism. *Horm Res Paediatr*. 2012;77:376-381. Epub 2012 Jun 12
17. Lazarus J, Brown RS, Daumerie C, Hubalewska-Dydejczyk A, Negro R, Vaidya B. 2014 European Thyroid Association Guidelines for the management of subclinical hypothyroidism in pregnancy and in children. *Eur Thyroid J*. 2014;3:76-94. Epub 2014 Jun 7
18. de Vries L, Bulvik S, Phillip M. Chronic autoimmune thyroiditis in children and adolescents: at presentation and during long-term follow-up. *Arch Dis Child*. 2009;94:33-37. Epub 2008 Aug 14
19. Neyzi O, Bundak R, Gökçay G, Günöz H, Furman A, Darendeliler F, Baş F. Reference values for weight, height, head circumference, and body mass index in Turkish children. *J Clin Res Pediatr Endocrinol*. 2015;7:280-293.
20. Baumgartner RN, Roche AF, Himes JH. Incremental growth tables: supplementary to previously published charts. *Am J Clin Nutr*. 1986;43:711-722.

21. World Health O, UNICEF, ICCIDD. Assessment of iodine deficiency disorders and monitoring their elimination: a guide for programme managers. Geneva: World Health Organization; 2007.
22. Lazar L, Frumkin RB, Battat E, Lebenthal Y, Phillip M, Meyerovitch J. Natural history of thyroid function tests over 5 years in a large pediatric cohort. *J Clin Endocrinol Metab*. 2009;94:1678-1682. Epub 2009 Feb 24
23. Catli G, Abaci A, Büyükgebiz A, Bober E. Subclinical hypothyroidism in childhood and adolescence. *J Pediatr Endocrinol Metab*. 2014;27:1049-1057.
24. Ergin Z, Savaş-Erdeve Ş, Kurnaz E, Çetinkaya S, Aycan Z. Follow-up in children with non-obese and non-autoimmune subclinical hypothyroidism. *J Pediatr Endocrinol Metab*. 2018;31:1133-1138.
25. De Luca F, Wasniewska M, Zirilli G, Aversa T, Arrigo T. At the end of a two-year follow-up elevated TSH levels normalize or remain unchanged in most the children with subclinical hypothyroidism. *Ital J Pediatr*. 2010;36:11.
26. Crisafulli G, Aversa T, Zirilli G, Pajno GB, Corica D, De Luca F, Wasniewska M. Subclinical hypothyroidism in children: when a replacement hormonal treatment might be advisable. *Front Endocrinol (Lausanne)*. 2019;10:109.
27. Wasniewska M, Salerno M, Cassio A, Corrias A, Aversa T, Zirilli G, Capalbo D, Bal M, Mussa A, De Luca F. Prospective evaluation of the natural course of idiopathic subclinical hypothyroidism in childhood and adolescence. *Eur J Endocrinol*. 2009;160:417-421. Epub 2008 Dec 12
28. Çatli G, Kir M, Anik A, Yilmaz N, Böber E, Abaci A. The effect of L-thyroxine treatment on left ventricular functions in children with subclinical hypothyroidism. *Arch Dis Child*. 2015;100:130-137. Epub 2014 Sep 10
29. Hunter I, Greene SA, MacDonald TM, Morris AD. Prevalence and aetiology of hypothyroidism in the young. *Arch Dis Child*. 2000;83:207-210.
30. Desai MP, Karandikar S. Autoimmune thyroid disease in childhood: a study of children and their families. *Indian Pediatr*. 1999;36:659-668.
31. Cappa M, Bizzarri C, Crea F. Autoimmune thyroid diseases in children. *J Thyroid Res*. 2010;2011:675703.
32. Moore DC. Natural course of 'subclinical' hypothyroidism in childhood and adolescence. *Arch Pediatr Adolesc Med*. 1996;150:293-297.
33. Radetti G, Maselli M, Buzi F, Corrias A, Mussa A, Cambiaso P, Salerno M, Cappa M, Baiocchi M, Gastaldi R, Minerba L, Loche S. The natural history of the normal/mild elevated TSH serum levels in children and adolescents with Hashimoto's thyroiditis and isolated hyperthyrotropinaemia: a 3-year follow-up. *Clin Endocrinol (Oxf)*. 2012;76:394-398.
34. Aversa T, Valenzise M, Corrias A, Salerno M, De Luca F, Mussa A, Rezzuto M, Lombardo F, Wasniewska M. Underlying Hashimoto's thyroiditis negatively affects the evolution of subclinical hypothyroidism in children irrespective of other concomitant risk factors. *Thyroid*. 2015;25:183-187. Epub 2014 Dec 2
35. Pearce EN. Iodine deficiency in children. *Endocr Dev*. 2014;26:130-138. Epub 2014 Aug 29
36. Chopra IJ, Hershman JM, Hornabrook RW. Serum thyroid hormone and thyrotropin levels in subjects from endemic goiter regions of New Guinea. *J Clin Endocrinol Metab*. 1975;40:326-333.
37. Delange F, Hershman JM, Ermans AM. Relationship between the serum thyrotropin level, the prevalence of goiter and the pattern of iodine metabolism in Idjwi Island. *J Clin Endocrinol Metab*. 1971;33:261-268.
38. Zimmermann MB, Aeberli I, Melse-Boonstra A, Grimci L, Bridson J, Chaouki N, Mbhenyane X, Jooste PL. Iodine treatment in children with subclinical hypothyroidism due to chronic iodine deficiency decreases thyrotropin and C-peptide concentrations and improves the lipid profile. *Thyroid*. 2009;19:1099-1104.
39. Meng F, Zhao R, Liu P, Liu L, Liu S. Assessment of iodine status in children, adults, pregnant women and lactating women in iodine-replete areas of China. *PLoS One*. 2013;8:e81294.
40. Aarsland TE, Aakre I, Stea TH, Henjum S, Markhus MW, Strand TA, Dahl L, Korevaar TI, Bakken KS, Sleire SN. Association of mild-to-moderate iodine deficiency with thyroid function-a systematic review and meta-analysis. *Adv Nutr*. 2025;16:100471. Epub 2025 Jul 8
41. Sabin MA, Kiess W. Childhood obesity: Current and novel approaches. *Best Pract Res Clin Endocrinol Metab*. 2015;29:327-338. Epub 2015 Apr 22
42. Niranjana U, Wright NP. Should we treat subclinical hypothyroidism in obese children? *BMJ*. 2016;352:i941.
43. Jin HY. Prevalence of subclinical hypothyroidism in obese children or adolescents and association between thyroid hormone and the components of metabolic syndrome. *J Paediatr Child Health*. 2018;54:975-980. Epub 2018 May 16
44. Rapa A, Monzani A, Moia S, Vivenza D, Bellone S, Petri A, Teofoli F, Cassio A, Cesaretti G, Corrias A, de Sanctis V, Di Maio S, Volta C, Wasniewska M, Tatò L, Bona G. Subclinical hypothyroidism in children and adolescents: a wide range of clinical, biochemical, and genetic factors involved. *J Clin Endocrinol Metab*. 2009;94:2414-2420. Epub 2009 May 5
45. Marras V, Casini MR, Pilia S, Carta D, Civolani P, Porcu M, Uccheddu AP, Loche S. Thyroid function in obese children and adolescents. *Horm Res Paediatr*. 2010;73:193-197. Epub 2010 Mar 3
46. Reinehr T. Obesity and thyroid function. *Mol Cell Endocrinol*. 2010;316:165-171. Epub 2009 Jun 18
47. Aeberli I, Jung A, Murer SB, Wildhaber J, Wildhaber-Brooks J, Knöpfli BH, Zimmermann MB. During rapid weight loss in obese children, reductions in TSH predict improvements in insulin sensitivity independent of changes in body weight or fat. *J Clin Endocrinol Metab*. 2010;95:5412-5418. Epub 2010 Sep 15
48. Longhi S, Radetti G. Thyroid function and obesity. *J Clin Res Pediatr Endocrinol*. 2013;5 (Suppl 1):40-44. Epub 2012 Nov 1
49. Walczak K, Sieminska L. Obesity and thyroid axis. *Int J Environ Res Public Health*. 2021;18:9434.
50. Radetti G, Gottardi E, Bona G, Corrias A, Salardi S, Loche S; Study Group for Thyroid Diseases of the Italian Society for Pediatric Endocrinology and Diabetes (SIEDP/ISPED). The natural history of euthyroid Hashimoto's thyroiditis in children. *J Pediatr*. 2006;149:827-832.