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Subclinical hypothyroidism in children and adolescents as mild dysfunction of the thyroid gland: a single-center study

Subkliniczna niedoczynność tarczycy u dzieci i młodzieży jako łagodna dysfunkcja gruczołu tarczowego – badanie jednoośrodkowe

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Abstract

Introduction: Subclinical hypothyroidism (SH) is a biochemical diagnosis made when a serum thyroid-stimulating hormone (TSH) is elevated with circulating thyroid hormone levels within their reference ranges.

Aim of the study: Aim of our prospective non-randomized study was to evaluate the course of SH.

Material and methods: All patients with suspicion of SH referred to the Endocrinology Outpatient Clinic between 2014 and 2018 were recruited to prospective study.

Results: A total of 130 patients with SH were recruited for this study. Thirty-five (26.9%) patients were followed up without levothyroxine (L-T4) (SH-T0 group) and therapy with L-T4 was randomly introduced in 95/130 (73.1%) SH children (SH-T1 group). We did not find statistical differences in ΔhSDS and BMI Z-score between the SH-T0 and SH-T1 groups ($p = 0.761$ and $p = 0.843$, respectively). Introducing L-T4 in patients with short stature did not affect the linear growth at the end of FU expressed as ΔhSDS. OH developed in six children (6.3%) in the SH-T1 group. After conducting a multivariate logistic regression, we found that the baseline TSH concentration and BMI Z-score are possible predictors of OH.

Conclusions: Our study confirmed a low risk of progression of SH to overt hypothyroidism. The majority of patients remains SH or resolved for normal thyroid function. The L-T4 therapy did not effect on linear growth and body weight. The main predictor of worsening to hypothyroidism were a higher TSH level and Z-score BMI.

Key words:
children, adolescents treatment, subclinical hypothyroidism, levothyroxine.

Streszczenie

Wprowadzenie: Subkliniczna niedoczynność tarczycy (SH) jest diagnozowana, gdy stężenie hormonu tyreotropowego w surowicy (TSH) jest zwiększone, a stężenie hormonów tarczycy mieści się w zakresie wartości referencyjnych.

Cel pracy: Celem naszego prospektywnego nierandomizowanego badania była ocena naturalnego przebiegu SH.

Materiał i metody: Do badania prospektywnego zakwalifikowano wszystkich pacjentów z podejrzeniem SH, którzy byli skierowani do Przyklinicznej Poradni Endokrynologicznej w latach 20142018.

Wyniki: Do badania włączono łącznie 130 pacjentów z SH. Trzydziestu pięciu (26,9%) pacjentów poddano obserwacji bez włączenia lewotyroksyny (L-T4) (grupa SH-T0), a terapię L-T4 wprowadzono losowo u 95/130 (73,1%) dzieci z SH (grupa SH-T1). Nie stwierdzono różnic statystycznych w zakresie ΔhSDS i BMI Z-score między grupami SH-T0 i SH-T1 (odpowiednio $p = 0{,}761$ i $p = 0{,}843$). Wprowadzenie L-T4 u pacjentów z niskim wzrostem nie wpłynęło na liniowy wzrost pod koniec FU wyrażony jako ΔhSDS. Progresję do OH obserwowano u 6 dzieci (6,3%) w grupie SH-T1. Po przeprowadzeniu wieloczynnikowej regresji logistycznej stwierdzono, że początkowo stężenie TSH i BMI Z-*score* są prawdopodobnymi predyktorami OH.

Wnioski: Badanie potwierdziło niskie ryzyko progresji SH do jawnej niedoczynności tarczycy. U większości pacjentów pod koniec obserwacji stwierdza się subkliniczną niedoczynność tarczycy lub eutyreozę. Terapia L-T4 nie wpłynęła na wzrost i masę ciała na końcu obserwacji. Głównymi predyktorami rozwoju jawnej niedoczynności tarczycy były: większe stężenie TSH i BMI Z-*score*.

Słowa kluczowe:
dzieci, młodzież, leczenie, subkliniczna niedoczynność tarczycy, lewotyroksyna.

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Introduction

Subclinical hypothyroidism (SH), a biochemical diagnosis, is made when serum thyroid-stimulating hormone (TSH) levels are elevated and circulating thyroid hormone levels are within their reference ranges [1, 2]. According to previous studies, the prevalence of SH in the pediatric population varies from 1.7% to 2.9% [3, 4]. The frequency of occurrence is higher in obese patients (7.5%) [5], as well as in genetically confirmed syndromes, such as trisomy 21 (Down syndrome, DS) or Turner syndrome (TS), approximately 25-32% to even 50-60% in patients with DS [6–8] and 19.2% in patients with TS [9]. It seems that vast majority of the patients are asymptomatic and become euthyroid during the observation period [10–12], and only a small percentage of patients progressed to an overt hypothyroidism is detected [11, 12]. Some studies highlight female sex, TSH exceeding 7.5 μIU/ml, and autoimmune diseases, especially elevated titers of thyroid peroxidase antibodies (TPOAb), as risk factors for overt hypothyroidism (OH) [4]. The best management of SH in children remains controversial. The decision to initiate treatment with levothyroxine (L-T4) strictly depends on the underlying cause of SH and is based on family and personal history, presence of symptoms suggesting hypothyroidism, physical examination, and potential assessment benefits of L-T4 substitution [13, 14].

We conducted a non-randomized prospective study in a population of generally healthy children diagnosed with SH (aged 3–18 years) recruited in an endocrinological outpatient clinic to evaluate the natural course of SH and determine the benefits of substitutional therapy with L-T4.

Material and methods

Inclusion and exclusion criteria

All patients with suspected subclinical thyroid gland disorders who were referred to the Endocrinology Outpatient Clinic of the Medical University of Silesia between 2014 and 2018 were recruited for this prospective study. The patients were followed up until the end of June 2019. The inclusion criteria were as follows: 1) children of both sexes, aged 3–18 years; 2) normal concentration of free thyroxine (fT4) with an increased concentration of TSH ($>$ 4.0 μIU/ml) in the serum, in the absence of symptoms that could suggest hypothyroidism; 3) provide written consent to participate in the study; 4) lack of comorbidities that could temporarily affect the above-mentioned laboratory parameters and/or thyroid function; and 5) negative anti-thyroid antibodies at baseline; 6) normal thyroid gland on ultrasonography; 7) a negative history of irradiation of the neck; 8) normal screening test results for congenital hypothyroidism; and 9) children from regions with proper supply of iodine. We excluded the following children from the study: 1) aged $<$ 3 years; 2) treated with drugs that may interfere with thyroid function (e.g., lithium, antiepileptic drugs, glucocorticoids, or iodinated drugs); 3) patients diagnosed with concomitant chronic and acute diseases; 4) patients who lost to follow-up; and 5) children whose parents did not consent to participate in the study. The decision regarding treatment with L-T4 was made during the first visit to the outpatient clinic. The minimum observation period was 24 months. This study was conducted following the Declaration of Helsinki and by the Ethics Committee of the Medical University of Silesia [resolution number Nr KNW/0022/KB1/32/13]. Informed consent was obtained from all patients (aged $>$ 16 years), their parents or legal guardians.

Clinical and biochemical measurements

The following data were collected: sex, age at the time of presentation of SH, auxological data (height and weight), serum concentrations of TSH and free thyroxine (fT4), titer of anti-thyroid autoantibodies (antiperoxidase [anti-TPO] and antithyroglobulin [anti-TG]), positive family history, absence or presence of clinical symptoms suggestive of thyroid disease, and length of follow-up. Serum TSH and fT4 concentrations were measured using a chemiluminescent immunometric assay. Concentrations of anti-thyroid peroxidase antibody (anti-TPOAbs) and autoantibodies to thyroglobulin (anti-TGAb) were determined using an enzyme-labeled chemiluminescent sequential immunometric assay. The reference level for fT4 is 11.5–22.7 pmol/l (0.8–1.9 ng/dl). Anti-TG and anti-TPOAbs were considered undetectable at levels below 40 and 35 IU/ml, respectively. A thyroid ultrasound was performed at least once during the follow-up period using Acuson Antares (Siemens Medical Solutions USA, Inc.) with a VFX 13-5 linear transducer. Diffuse low echogenicity is considered an indicator of an autoimmune thyroid disorder. SH was diagnosed in patients without an evident clinical manifestation of hypothyroidism, regardless of age, if TSH was more than 4.0 μIU/ml in at least two consecutive assays and fT4 remained within the normal range. OH was diagnosed if, simultaneously, TSH was higher than 10.0 μIU/ml and fT4 was below the lower limit of the reference range. Thyroid autoimmunity was documented by the presence of thyroid autoantibodies (anti-TPO and/ or anti-TG antibodies). Hashimoto's thyroiditis (autoimmune thyroid disease) was diagnosed in the presence of anti-TPO and/or anti-TG antibodies, with different presentation patterns: subclinical or overt hypothyroidism or euthyroidism.

A standard stadiometer was used to measure the height of the patient. Height standard deviation scores (hSDS) were calculated from population standards for healthy children using the following formula: hSDS = child's height − height for 50 pc/0.5 × (height 50 pc − height 3 pc). Short stature was defined as an hSDS below the (–2.0) standard deviation (SD). Body mass index (BMI) was expressed in kg/m^2. Given a child's age, sex, BMI, and the appropriate reference standard, the BMI Z-score was calculated using the Pediatric Z-Score Calculator. The tool is available on the website of The Children's Hospital of Philadelphia, Research Institute: https://zscore.research.chop.edu/calcbmi.php and is dedicated to patients aged 2–20 years [15]. A BMI Z-score greater than +2.0 SD was classified as obesity, between +2.0 and +1.0 SD as overweight, between –1.0 and –2.0 SD as weight deficiency, and under –2.0 SD as significant weight deficiency [16]. Changes in linear growth and body weight during observation were expressed as ΔhSDS Z-score and ΔBMI, respectively.

The difference in TSH concentration between the last and first determinations was defined as ΔTSH. Data are displayed as mean ± SD and range.

Study design

Clinical condition, patient complaints anthropometric and biochemical measurements data were collected during regular physical examinations every 3-6 months or anamnesis during the visit. Patients were in non-randomized way divided to one of the two intervention groups. Group SH-T0 did not receive levothyroxine while children from group SH-T1 received levothyroxine. The decision regarding treatment with L-T4 was made during the first visit to the outpatient clinic. The minimum observation period was 24 months.

Statistical analysis

Calculations were performed using StatPlus: mac Pro [17]. Numerical data are expressed as mean ± SD or median and range values, as appropriate. Categorical variables were presented as frequencies and percentages. The Shapiro-Wilk test was used to assess the normality of the distribution. Data with a normal distribution were analyzed using *t*-tests and those without a normal distribution were analyzed using the Mann–Whitney *U* test. Linear Spearman's correlation was used to investigate possible relationships between BMI Z-score and TSH concentrations. We used the Wilcoxon test to compare the parameters at baseline and the end of the follow-up period. A receiver operating characteristic (ROC) curve was constructed to assess the TSH cutoff value. Stepwise logistic regression was used for multivariate analysis to establish independent predictors of progression to OH at the end of the follow-up period. The p-value < 0.05 was considered significant.

Results

A total of 130 patients (76/130 females, 58.5%) with elevated TSH concentrations and normal free hormones were recruited for this study and observed until the end of June 2019. Tables I and II present the clinical, anthropometric, and laboratory parameters of patients diagnosed with SH. Thirty-five (26.9%) patients were followed up without intervention (SH-T0 group), and substitutional therapy with L-T4 was randomly introduced in 95/130 (73.1%) SH children (SH-T1 group). The groups of males and females were similar in relation to the mean age at baseline, length of follow-up, TSH and fT4 concentrations, and anthropometric parameters (hSDS and BMI Z-score).

We did not find statistical differences in ΔhSDS and ΔBMI Z-score between the SH-T0 and SH-T1 groups ($p = 0.761$ and $p = 0.843$, respectively). Short stature was diagnosed in 4/35 (11.4%) children in the SH-T0 group and 12/95 (12.6%) children in the SH-T1 group ($p = 0.44$). Introducing L-T4 therapy in patients with short stature did not affect the linear growth at the end of follow-up expressed as ΔhSDS between the SH-T0 and SH-T1 groups (0.5 ±0.3, range 0.1-1.2 vs. 1 0.4 ±0.6, range: from –0.3 to 1.0; $p = 0.862$).

Overweight and obese patients with SH were higher (0.7 ±1.3; range: from –2.4 to 3.5) than those with normal weight (–0.3 ±1.6; range: from –5.1 to 4.3), and the difference was sta-

Table I. Comparison of measurements between SH patients with non-treated (SH-T0) and treated with levothyroxine (SH-T1)

Parameter	SH ($n = 130$) Mean ± SD (range)	SH-T0 ($n = 35$) Mean ±SD (range)	SH-T1 ($n = 95$) Mean ±SD (range)	p-value (* significance between SH-T0 and SH-T1)
F, *n* (%)	76 (58.5)	22 (62.9)	54 (56.8)	0.851
Age at baseline (years)	9.5 ±3.1 (3.3–15.1)	9.2 ±3.0 (3.5–15.1)	9.5 ±3.2 (3.1–15.1)	0.619
Age at end of FU (years)	12.7 ±3.3 (5.5–18.0)	12.0 ±3.7 (5.5–18.0)	12.7 ±3.5 (5.8–18.0)	0.327
Length of FU (months)	38.3 ±16.6 (24.0–99.3)	37.3 ±15.4 (24.0–78.0)	38.5 ±17.3 (24.0–99.3)	0.157
TSH (μIU/ml) at baseline	6.3 ±3.2 (4.0–25.2)	5.7 ±1.7 (4.1–9.4)	6.6 ±4.0 (4.0–25.2)	0.440
TSH (μIU/ml) at the end of FU	3.8 ±1.9 (1.1–13.3)	4.2 ±1.4 (1.2–8.0)	3.7 ±2.2 (1.0–13.3)	**0.006***
fT4 (ng/dl) at baseline	1.2 ±0.2 (0.8–1.7)	1.2 ±0.2 (1.0–1.6)	1.2 ±0.3 (0.8–1.7)	0.432
fT4 (ng/dl) at the end of FU	1.2 ±0.02 (0.8–1.8)	1.2 ±0.2 (0.9–1.5)	1.3 ±0.2 (0.7–1.8)	0.053
Positive family history, *n* (%)	48 (36.9)	18 (60.0)	30 (31.6)	0.671

SH – subclinical hypothyroidism; SH-T0 – patients with subclinical hypothyroidism without treatment; SH-T1 – patients with subclinical hypothyroidism treated with levothyroxine; N-number; FU – follow-up; TSH – thyroid-stimulating hormone; fT4 – free thyroxine

Table II. Comparison of anthropometric data between SH patients: non-treated (SH-T0) and treated with levothyroxine (SH-T1)

Parameter	SH (n = 130) Mean ± SD (median; IQR)	SH-T0 (n = 35) Mean ±SD (median; IQR)	SH-T1 (n = 95) Mean ±SD (median; IQR)	p-value (* significance between SH-T0 and SH-T1)
hSDS at baseline	–0.1 ±1.6 (0.0; from –1.2 to 1.0)	–0.3 ±1.4 (–0.4; from –1.4 to 0.6)	0.0±1.7 (0.2; from –1.1 to 1.2)	0.315
ΔhSDS	0.0±0.7 (0.1; from –0.3 to 0.5)	0.1 ±0.9 (0.2; from –0.2 to 0.4)	0.0 ±0.8 (0.1; from –0.3 to 0.5)	0.843
BMI Z-score at baseline	0.3 ±1.3 (0.2; from –0.9 to 1.3)	0.2 ±1.2 (0.2; from –0.5 to 1.0)	0.3 ±1.4 (0.3; from –0.9 to 1.4)	0.769
ΔBMI Z-score	0.0±0.6 (–0.1; from –0.4 to 0.2)	0.0 ±0.5 (0.0; from –0.4 to 0.3)	0.0 ±0.7 (0.1; from –0.4 to 0.2)	0.761

hSDS – height standard deviation score; BMI – body mass index; N – number; SD – standard deviation

tistically significant ($p < 0.005$). The frequency of normalization of TSH levels (TSH < 4 μIU/ml) was comparable in overweight and obese children without L-T4 intervention (SH-T0 group) and who had L-T4 treatment (SH-T1 group): 15/21 (71.4 %) vs. 14/21 (66.7%), $p = 0.34$. There was no relationship between ΔTSH and ΔBMI Z-scores in overweight and obese children in the SH-T0 ($p = 0.14$, $rho = –0.34$) and SH-T1 groups ($p = 0.51$, $rho = 0.15$).

Eighteen (18/35, 51.4%) patients in the SH-T0 group and 58/95 (61.1%) in the SH-T1 group had normal thyroid function at the end of the FU. Meanwhile, SH persisted in 31/95 (32.6%) children in the SH-T1 group; 28 cases with TSH levels remained within 4.0–10.0 μIU/ml, while the remaining (3 cases) was > 10 μIU/ml. OH developed in six children (6.3%) in the SH-T1 group.

The anti-TPO and/ or anti-TG antibodies were detected at the end of FU in 27 cases (SH-T1): anti-TPO and or anti-TG antibodies in 12/27 cases, only anti-TPO in 14/27 and only anti-TG antibodies in 1/27 case.

In Table III, we compared patients in the SH-T1 group who worsened to OH at the end of FU (only in the SH-T1 group) and those who remained with SH. After conducting a multivariate logistic regression, we found that the baseline TSH concentration and BMI Z-score are possible predictors of OH (Table IV). ROC curve showed a TSH cutoff value of 7.2 μU/l (AUC 0.912) with the maximized sensitivity of 100% and specificity of 78.8 % in identifying OH.

Discussion

To the best of our knowledge, this is the first prospective non-randomized study which evaluate the effects of L-T4 treatment in a Polish pediatric population and the evolution of SH over time. It is unanimous that L-T4 supplementation should be initiated in children with TSH ≥ 10 μU/l. However, there is no consensus regarding TSH levels of 4.5–9.9 μIU/ml. Some studies believe that L-T4 therapy should be considered when subjective or objective syndromes of hypothyroidism and/or proatherogenic metabolic abnormalities are present, as well as in infants and children up to 3 years of age (in newborns with TSH levels between 6 and 20 μIU/l). Moreover, introduction of the L-T4 treatment should be recommended for children with SH and Hashimoto's thyroiditis, goiter as well as progressive deterioration of thyroid gland function over time. Replacement of L-T4 is recommended in the presence of diabetes mellitus, celiac disease, genetic disorders such as: trisomy 21 and in Turner syndrome [8]. The treatment is not advisabled in children with idiopathic and mild SH, negative anti-thyroid autoantibodies, no goiter and no evidence of Hashimoto thyroiditis at ultrasonography [14].

According to the literature data, different TSH cut-off limits have been reported in population-based studies conducted by various countries researchers: Radetti *et al.* diagnosed SH when serum TSH was > 3.6 μIU/ml [18], Kumar *et al.* when TSH level was > 4.0 μIU/ml [19], Grandone *et al*. when serum TSH was > 4.2 μIU/l [20], Cerbone *et al.* when serum TSH was more than > 4.5 μIU/l [21]. Following the Salerno [13], the upper concentration of the normal range for TSH should be placed between 4.0–5 μU/l, but considerable differences exist in pediatric population. Recognition of the value of TSH concentration 4.5-5 μIU/l as the upper limit may cause overdiagnosis of SH in children because the upper limit of the TSH concentration corresponding to the 97th percentile is significantly higher in children up to 14 years old, as shown by Kapelari *et al.* in population studies [22]. In our center, we decided to adopt the upper limit of normal as 4.0 μIU/ml.

Moreover, the majority of patients with SH in our study were female, which is consistent with the literature [1, 2, 23]; however, contrary to previous publications, sex was not a predictive factor for developing OH in our study.

Table III. Comparison of baseline parameters between SH-T1 patients who develop OH and with persistent SH at the end of follow-up

Parameter	OH (n = 6) Mean ±SD (range)	Persistent SH (n = 31) Mean ±SD (range)	p-value (* significance)
Age (years)	8.5 ±1.6 (6.1–9.7)	9.4 ±3.2 (3.3–14.5)	0.52
Sex (F), n (%)	4 (66.7)	17 (54.8)	0.48
TSH (μIU/ml) baseline	11.6 ±3.8 (7.5–17.7)	6.4 ±2.6 (4.4–13.1)	**0.002***
fT4 (μIU/ml) baseline	0.0±0.1 (0.9–1.0)	1.2 ±0.2 (0.8–1.7)	0.15
BMI Z-score baseline	1.2 ±0.7 (0.0–2.0)	–0.1 ±1.4 (from –0.3 to 1.9)	**0.03***
ΔBMI Z-score	–0.1 ±0.4 (from –0.8 to 0.3)	0.2 ±0.9 (from –2.2 to 2.1)	0.47
hSDS baseline	0.3 ±0.7 (from –1.0 to 1.0)	0.0 ±1.5 (from –2.9 to 4.3)	0.59
ΔhSDS	0.2 ±0.5 (from –0.3 to 0.7)	0.1 ±1.9 (from –2.2 to 2.9)	0.73
Abs (+), n (%)	1 (16.7)	11 (35.5)	0.10

SH – subclinical hypothyroidism; OH – patients with overt hypothyroidism; F – female sex; N – number; SD – standard deviation' FU – follow-up; TSH – thyroid-stimulating hormone, fT4 – free thyroxine; hSDS – height standard deviation score; BMI – body mass index; Abs – antithyroid autoantibodie

Impact on linear growth

Our study provides further evidence that L-T4 therapy does not have a positive effect on linear growth in children. At the end of the FU, the changes in body height were comparable between the two groups (SH-T0 and SH-T1). For more than 100 years, TSH and thyroid hormones have been established to play an essential role in the regulation of bone growth and maturation by direct influence on the skeletal or due to their impact on the activity of the growth hormone-insulin-like growth factor 1 (GH-IGF-1) axis [24, 25]. Therefore, the impact of thyroid dysfunction on bone has been widely studied and short stature and abnormal bone maturation are considered as consequences of untreated hypothyroidism. We found only a few prospective studies; most of the long-term publications available were retrospective. A comparable height velocity was found by Wasniewska *et al.* during a 2-year prospective observation period in children with and without SH [26]. Another study by Cerbone *et al.* supported this hypothesis [25] – they compared 36 children with long-running mild SH and age-matched controls regarding height, growth velocity, and bone maturation and did not find differences. Another studies showed a lack of influence on linear growth and bone maturation [27–29].

Overweight and obesity in patients with SH

In overweight and obese children, the prevalence of SH is estimated to be 7–23% [30, 31]. The proposed mechanism of this phenomenon is the effect of leptin on the hypothalamic-pituitary axis, which influences the secretion of thyrotropin-releasing hormone and, subsequently, TSH and peripheral thyroid hormone secretion. Leptin, a known fat tissue hormone produced by adipocytes, is strictly proportional to adiposity [32]. In our study, we compared patients with excess and normal body weight for more detailed analyses. The other parameters were

Table IV. Logistic regression analysis for predictors for overt hypothyroidism (OH)

Parameter	Odds ratio	95% CI	p-value (* significance)
Age	0.64	0.28–1.47	0.94
F gender	0.17	0.05–0.22	0.42
Goiter	0.37	0.08–0.74	0.91
ΔhSDS	1.49	0.41–5.51	0.54
BMI Z-score	2.81	0.47–16.65	**0.045**
TSH level	1.45	1.03–2.04	**0.003**
fT4	0.14	0.01–0.66	0.82
Positivity of Abs	0.29	0.05–0.73	0.69

OH – patients with overt hypothyroidism; F – female sex; TSH – thyroid-stimulating hormone; fT4 – free thyroxine; Abs – antithyroid autoantibodies; hSDS – height standard deviation score; BMI – body mass index

comparable except for the difference in the ΔhSDS. According to some publications [19, 29, 33–35] treatment does not affect body weight changes, while weight loss may normalize TSH levels [20, 35]. It is widely believed that increases in TSH concentration are a consequence of excessive weight gain rather than a cause of dysfunction of the thyroid gland [20, 36–38]. In our analysis, therapeutic intervention with L-T4 in overweight and obese children with SH was not significantly correlated with changes in BMI Z-score and TSH concentrations. Similar results were achieved in children who did not receive L-T4 treatment. In the absence of clinical and laboratory markers of OH, treatment with L-T4 is unnecessary [19]. However, in our study, overweight and obesity posed a risk of developing OH, which has been confirmed in the literature [39].

Normalization of TSH levels and deterioration to OH over time

The available literature has shown that the most common natural history of SH is spontaneous normalization of TSH or persistence of elevated TSH, rarely progression to an overt thyroid disorder. According to several studies, 38.9% [10], 41.3%, [26], or even 89% of children became euthyroid over time, while the ratio of maintaining SH varied from 55.6% [10] to 58.7% [26]. In our cohort, most of the patients became euthyroid (51.4% in the SH-T0 group and 61% in the SH-T1 group), while 48.6% and 32.6% of patients in the SH-T0 and SH-T1 groups, respectively, maintained elevated TSH.

Many studies attempted to answer whether SH could be considered a variant of normal thyroid function or a mild, transient dysfunction or disorder that might involve the worsening of OH. The progression ratio of OH in children without underlying conditions such as genetic syndromes varies (0–28.8%) [10, 40, 41]. In our study, the deterioration of thyroid function occurred in 4.6% of patients, which did not differ from the literature. Radetti *et al*. [41] conducted a study that initially recognized goiter and elevated antithyroglobulin antibody titers as risk factors for deteriorating thyroid function. In contrast, in 2009, Lazar *et al*. conducted a large 5-year long-term retrospective study that concluded that during the observation period, there was a tendency for TSH to normalize, and the predictive factors for the development of OH were only higher baseline TSH levels (> 7.5 μIU/ml) and female sex [4]. According to Murillo-Valles *et al*., baseline TSH concentration, female sex and the presence of anti-thyroid autoantibodies were risk factors for progression to OH [42]. In the study conducted by Aversa [43], it was found that children with mild and HT-related SH have a high risk of a progression to OH over time (53.1%), whereas the probability of spontaneous TSH normalization is relatively low (21.9%).

In our analysis, we found that only a high TSH level and higher BMI Z-score at baseline predicted the development of OH.

Limitations

Our study has several limitations, that is, the duration of follow-up, the single-center nature of the clinical trial with a limited number of patients and the lack of randomization.

Conclusion

Our study confirmed a low risk of progression from a subclinical thyroid disorder to OH. Most patients sustained SH or have resolved to normal thyroid function. Substitutional L-T4 therapy did not positively affect linear growth or body weight. The main predictors of worsening hypothyroidism were a higher TSH level and BMI Z-score. Thyroid autoimmunity and a positive family history of thyroid gland disorders did not predispose patients to progression to OH.

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