ABSTRACT

Objective: The aim of this study is to look at the relationship between hyperthyrotropinemia and anthropometric measurements as well as cardiometabolic risk factors in obese children and adolescents.

Materials and Methods: A total of 100 patients with isolated hyperthyrotropinemia and 124 patients with normal thyroid functions, between 10 and 18 years of age, were included in the study. Anthropometric and blood pressure measurements and biochemical parameters were recorded. Non-high-density lipoprotein cholesterol, total cholesterol/high-density lipoprotein cholesterol, and triglyceride/high-density lipoprotein cholesterol ratios were calculated.

Results: The subjects’ mean age was 12.6 ± 1.9 years and their mean body mass index was 29.8 ± 4 kg/m². The isolated hyperthyrotropinemia group had considerably greater levels of triglyceride, non-high-density lipoprotein cholesterol, and the triglyceride/high-density lipoprotein cholesterol ratio. Higher prevalences of hypertriglyceridemia and increased triglyceride/high-density lipoprotein cholesterol ratio were found in the group with isolated hyperthyrotropinemia. Thyroid-stimulating hormone had a statistically significant positive relationship with triglyceride, non-high-density lipoprotein cholesterol, total cholesterol/high-density lipoprotein cholesterol ratio, and triglyceride/high-density lipoprotein cholesterol ratio, as well as an inverse relationship with high-density lipoprotein cholesterol. Thyroid-stimulating hormone was positively correlated with triglyceride and triglyceride/high-density lipoprotein cholesterol ratio in both females and males; however, only in females, thyroid-stimulating hormone was positively correlated with non-high-density lipoprotein cholesterol and total cholesterol/high-density lipoprotein cholesterol ratio. The triglyceride/high-density lipoprotein cholesterol ratio, as well as the rates of hypertriglyceridemia were higher in children with isolated hyperthyrotropinemia in the female subgroup. Male children with isolated hyperthyrotropinemia had significantly higher triglyceride levels in comparison with males with normal thyroid-stimulating hormone.

Conclusion: The present study suggested that isolated hyperthyrotropinemia is associated with adverse effects on lipid metabolism in obese children and adolescents, especially in females.

Keywords: Obesity, isolated hyperthyrotropinemia, children and adolescents, dyslipidemia.

INTRODUCTION

Obesity has been associated with an increased risk of metabolic and cardiovascular problems such as impaired glucose metabolism, hypertension, dyslipidemia, and endothelial dysfunction. Thyroid hormones play a role in lipid and glucose metabolism, which helps to regulate basal metabolism, modulate appetite and food intake, and regulate body weight.
Thyroid dysfunction causes changes in BW and composition; but, in the majority of obese children and adolescents, thyroid function is deemed normal. In children with obesity, recent investigations have found higher serum thyroid-stimulating hormone (TSH) levels despite normal or slightly elevated free thyroxine (fT4) and/or free triiodothyronine (fT3) levels. While weight loss causes high thyroid hormone levels to return to normal, treatment with levothyroxine (LT4) does not induce weight loss in patients with obesity. These alterations in thyroid function seem like a consequence rather than being a cause of obesity. Therefore, this condition is frequently defined as isolated hyperthyrotropinemia (IH) rather than subclinical hypothyroidism (SCH). The real cause of IH in subjects with obesity is not fully understood and is likely multifactorial. It is thought to be a strategy for improving resting energy consumption in order to avoid further weight gain. Increased TSH levels have been linked to cardiometabolic risk factors such as dyslipidemia, hypertension, ischemic heart disease, metabolic syndrome (MetS), and insulin resistance (IR) even when they are within the “euthyroid” range in adult and some pediatric studies, but the findings are inconsistent.

Thyroid hormones are involved in regulating lipid synthesis, metabolism, and mobilization. They increase cholesterol synthesis in the liver and the expression of the cell surface low-density lipoprotein cholesterol (LDL-c) receptor in the liver and other tissues while reducing cholesterol absorption from the intestines. Additionally, thyroid hormones increase the concentration of cholesterol ester transfer protein (CETP) and the activity of hepatic lipase and lipoprotein lipase, thereby affecting high-density lipoprotein cholesterol (HDL-c), and triglyceride (TG) levels. There are many studies that show that elevated TSH, even in the normal serum concentration range, can affect lipid metabolism. However, the effect of IH on a serum lipid profile in obese children and adolescents remains unclear, as the findings of a small number of studies available are contradictory. The differences in study results indicate a lack of clarity in the literature regarding the effect of IH on lipid metabolism in obese patients.

The objective of this study is to examine the association of hyperthyrotropinemia with anthropometric measurements and cardiometabolic risk factors including blood pressure (BP) and glucose and lipid metabolism in obese children and adolescents. We investigated the relationship between TSH and serum lipid concentrations including total cholesterol (TC), TG, LDL-c, and HDL-c, also evaluating sex-specific differences in detail.

**MATERIALS AND METHODS**

**Participants**

Two hundred twenty-four obese children and adolescents (123 females and 101 males) who were evaluated in the Pediatric Endocrine Clinic participated in the study. A total of 100 patients with IH and 124 participants with normal thyroid functions served as the euthyroid control group and were included in the study. The characteristics of the groups were similar in terms of age and sex. Isolated hyperthyrotropinemia was determined to be a serum TSH level between 4.5 mIU/L and 9.9 mIU/L, having no indications or symptoms of hypothyroidism with normal fT3 and fT4 levels. The presence of a TSH level between 0.3 mIU/L and 4.5 mIU/L was classified as an euthyroid state with normal fT4 levels. Hospital records of obese

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**Figure 1.** Flowchart for the study population. TSH, thyroid-stimulating hormone.
patients who applied to the Pediatric Endocrine outpatient clinic between April 2017 and April 2019 were reviewed retrospectively. One hundred ten patients with elevated TSH were detected. One hundred twenty-nine euthyroid patients were randomly selected as a control group. The characteristics of 224 patients eligible according to the inclusion and exclusion criteria were recorded. Patients with IH and euthyroidism were divided into 2 groups (Figure 1).

The study was carried out in accordance with the Helsinki Declaration, and the study was authorized by the Institutional Review Board (decision number: 2018/18–08, date: December 6, 2018).

Inclusion and Exclusion Criteria
Inclusion criteria were age between 10 and 18 years, body mass index (BMI) ≥ 95th percentile (P) in terms of age and sex. Any syndrome or chronic disease known to impact body composition or fat distribution, as well as any significant illness since birth, presence of overt hypothyroidism, antithyroid peroxidase (anti-TPO) or antithyroglobulin (anti-TG) positive autoimmune thyroid illness or goiter, and drug use (LT4, glucocorticoids, metformin, etc.) were all considered exclusion criteria. Patients with known dyslipidemia or a history of diseases that could affect the lipid profile such as diabetes mellitus, kidney disease, rheumatological diseases, and other endocrine diseases were also excluded from the study. Patients with TSH levels ranging from 0.3 IU/L to 9.9 IU/L were included in the study. As a result, patients with TSH levels below 0.3 IU/L and above 10 IU/L were excluded.

Physical Examination
Measurements were taken while standing without shoes and wearing light clothes. A Harpenden stadiometer with a sensitivity of 0.1 cm, and BW was measured with a SECA scale with a sensitivity of 0.1 kg. Dividing weight (kg) by square meter of height (m²) resulted in the calculation of BMI. Age and sex-specific BMI percentiles and standard deviation scores (SDS) were derived from national references by the Child Metrics. The midpoint between the lowest costal ridge and the upper border of the iliac crest was used to measure waist circumference (WC), and the biggest circumference between waist and knee was used to assess hip circumference (HC). The waist-to-hip ratio (WHR) and the waist-to-height ratio (WHtR), which are both considered as metabolic risk indicators, were then computed. After a 5-minute rest, diastolic blood pressure (DBP) and systolic blood pressure (SBP) were taken in the supine position using a standard mercury sphygmomanometer with an appropriate-sized cuff to the nearest 2 mmHg in the right arm. Pubertal stage was defined using Tanner’s classification. A single endocrine specialist performed all of the physical examinations.

Biochemical Assessment
Early morning blood samples, after overnight fasting, were obtained for the measurement of glucose, insulin, lipids (TC, TG, LDL-c, and HDL-c), aspartate aminotransferase, alanine aminotransferase, and thyroid hormones (TSH, fT3, and fT4). Thyroid autoantibodies (anti-TPO and anti-TG) were tested in children with increased TSH levels.

Definitions
Obesity was defined as having a BMI of 95th P for both sex and age. The presence or absence of central obesity was determined using waist circumference percentiles (WC ≥ 95th P).20 For age, sex, and height, hypertension was defined as systolic or diastolic BP readings >95th P.21 The insulin resistance was determined using the fasting insulin (U/L) x fasting glucose (mmol/L)/22.5 homeostasis model assessment of IR (HOMA-IR).22,23 To identify the state of IR, different HOMA-IR cut-off values were employed for prepubertal and pubertal stages (prepubertal > 2.5, pubertal > 4).24 Our patients were diagnosed with MetS based on the International Diabetes Federation criteria for MetS diagnosis in children and adolescents,25 if they had abdominal obesity (WC 90th P for ages 16 years, and 94 cm for males and 80 cm for females for ages >16 years) and 2 or more of the risk factors listed below (1); For all ages, fasting blood glucose readings of more than 100 mg/dL (5.6 mmol/L) or previously diagnosed type-2 diabetes (2); For those under the age of 16, a blood TG level of 150 mg/dL (1.7 mmol/L) is required, and for those beyond the age of 16, the same cutoff or particular treatment for this lipid anomaly is required (3); decreased HDL-c: 40 mg/dL (1.03 mmol/L) for males and females under the age of 16, and 40 mg/dL for males and 50 mg/dL (1.29 mmol/L) for females over the age of 16, or particular treatment for this lipid anomaly (4); SBP 130 mmHg or DBP 85 mmHg for those under the age of 16, and the same cut off or treatment of previously diagnosed hypertension for those over the age of 16.

The National Heart, Lung, and Blood Institute’s Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents characterized abnormal lipid levels as TC ≥ 200 mg/dL, HDL-c < 40 mg/dL, and non-HDL-c ≥ 145 mg/dL.26 The following formula was used to determine non-HDL-c: Non-HDL-c = TC – HDL-c. Low-density lipoprotein cholesterol levels of > 130 mg/dL were defined as elevated.27 Triglyceride levels > 150 mg/dL were defined as hypertriglyceridemia.25 Total cholesterol/HDL-c ratio of > 5 is considered as a cardiac risk ratio (CRR).27 TG/HDL-c ratio > 3 was also considered as an atherogenic risk ratio (ARR).28 The cardiac risk ratio and ARR are considered indexes of severe cardiovascular risk.29,30

Statistical Analysis
The study data were analyzed using IBM 20.0 Statistical Package for Social Sciences version. The level of significance was determined to be P ≤ .05. Normal distribution was tested using the Kolmogorov–Smirnov test. Between-group comparison for categorical variables was performed by using the chi-square test or Fisher’s exact tests. Student’s t-tests and Mann–Whitney U test were used for the comparison of continuous variables. Continuous variables were expressed as mean ± standard deviation (SD) and median (minimum–maximum). Categorical variables were expressed as numbers and percentages. Correlations were investigated using Pearson and Spearman correlation test. The strength of the relationship was assessed by evaluating the numerical value of the correlation coefficient between −1 and +1.
RESULTS

In this study, 224 children and adolescents with obesity were evaluated. The subjects’ mean age was 12.6 ± 1.9 years and their mean BMI was 29.8 ± 4 kg/m². One hundred twenty-three (55%) subjects were female and 197 (89%) subjects were pubertal. The mean TSH was 4 ± 1.8 μIU/mL. The group with IH (TSH > 4.5 μIU/mL) included 100 (45%) and the group with normal thyroid functions (TSH between 0.3 μIU/mL and 4.5 μIU/mL) included 124 (55%) patients with obesity.

The Clinical and Biochemical Characteristics of the Study Groups

The study and control groups’ clinical and biochemical parameters were compared and Table 1 shows the results. In terms of age, sex, puberty stage, anthropometric, and BP measurements, there were no significant differences between the groups. Subjects with IH had significantly higher TSH levels as expected, additionally higher TG, non-HDL-c, and TG/HDL-c ratio compared with those with normal thyroid functions (P ≤ .001, .007, .048, and .008, respectively). In terms of other

| Variables | Patients with Obesity and Isolated Hyperthyrotropinemia n = 100 | Patients with Obesity and Normal Thyroid Function n = 124 | P |
|-----------|---------------------------------------------------------------|----------------------------------------------------------|---|
| **Clinical characteristics** | | | |
| Age (years) | 12.2 (10-17.9) | 12.6 (10-17.4) | .999<sup>a</sup> |
| Sex (female, %) | 58 (42%) | 65 (52.4%) | .404<sup>b</sup> |
| Puberty stage (pubertal, %) | 84 (84%) | 113 (91.1%) | .103<sup>c</sup> |
| Body weight (kg) | 74 ± 15.9 | 77.2 ± 16.5 | .143<sup>c</sup> |
| Body weight SDS | 2.26 (1.09-5.76) | 2.37 (0.9-5.84) | .389<sup>o</sup> |
| Body height (cm) | 157.7 ± 9.1 | 159 ± 10.3 | .243<sup>c</sup> |
| Body height SDS | 0.66 ± 1.04 | 0.79 ± 1.01 | .380<sup>o</sup> |
| BMI (kg/m²) | 29.45 ± 4.1 | 30.14 ± 3.98 | .206<sup>o</sup> |
| BMI SDS | 2.17 (1.61-4.08) | 2.2 (1.66-4.63) | .313<sup>o</sup> |
| BMI P | 98.4 (95.3-99.9) | 98.6 (95.1-99.9) | .232<sup>o</sup> |
| WC (cm) | 96.3 ± 9.8 | 98.3 ± 9.7 | .169<sup>o</sup> |
| HC (cm) | 104.2 ± 10.9 | 105.1 ± 9.79 | .548<sup>o</sup> |
| WHR | 0.93 ± 0.06 | 0.94 ± 0.06 | .227<sup>o</sup> |
| WHR | 0.6 ± 0.05 | 0.61 ± 0.05 | .289<sup>o</sup> |
| SBP (mmHg) | 110 (90-150) | 110 (90-160) | .064<sup>o</sup> |
| DBP (mmHg) | 87.8 (28.4-157) | 86 (21.5-208) | .661<sup>o</sup> |
| **Biochemical characteristics** | | | |
| FT3 (pg/mL) | 4.24 ± 0.56 | 4.29 ± 0.57 | .551<sup>c</sup> |
| FT4 (ng/dL) | 1.21 ± 0.13 | 1.23 ± 0.15 | .409<sup>c</sup> |
| FT3/FT4 | 3.55 (2.08-5.42) | 3.43 (2.23-5.59) | .350<sup>o</sup> |
| TSH (μIU/mL) | 5.53 (4.5-9) | 2.54 (0.94-4.49) | <.001<sup>o</sup> |
| Fasting glucose (mg/dL) | 89.7 ± 6.8 | 89.2 ± 6.9 | .561<sup>o</sup> |
| Fasting insulin (μU/mL) | 20.95 (5.73-62.2) | 21.7 (4.3-65) | .459<sup>o</sup> |
| HOMA-IR | 4.7 (1.3-16.3) | 4.8 (0.9-15.9) | .550<sup>o</sup> |
| TC (mg/dL) | 163 ± 31.8 | 158.5 ± 30.6 | .287<sup>o</sup> |
| TG (mg/dL) | 117 (44.7-344) | 91.7 (35-335) | .007<sup>o</sup> |
| LDL-c (mg/dL) | 87.8 (28.4-157) | 86 (21.5-208) | .661<sup>o</sup> |
| HDL-c (mg/dL) | 44.4 (23-82) | 45.7 (27.6-90.8) | .172<sup>o</sup> |
| Non-HDL-c | 118.6 (51-189.7) | 105.2 (30.5-235.1) | .048<sup>o</sup> |
| TC/HDL-c ratio | 3.59 (1.64-7.14) | 3.31 (1.53-6.95) | .069<sup>o</sup> |
| TG/HDL-c ratio | 2.56 (0.56-13.76) | 2.10 (0.51-6.83) | .008<sup>o</sup> |
| AST (IU/L) | 19 (10-142) | 20 (8-84) | .074<sup>o</sup> |
| ALT (IU/L) | 17.5 (5-263) | 20 (7-186) | .136<sup>o</sup> |

<sup>a</sup>Mann–Whitney U test; Data are given as median (minimum-maximum).
<sup>b</sup>Chi-square test; Data are given as a percentage (%).
<sup>c</sup>Student T test; Data are given as mean ± SD.
The bold P values are statistically significant.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; DBP, diastolic blood pressure; FT3, free triiodothyronine; FT4, free thyroxine; HC, hip circumference; HDL-c, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; LDL-c, low-density lipoprotein cholesterol; P, percentile; SBP, systolic blood pressure; SDS, standard deviation score; TC, total cholesterol; TG, triglyceride; TSH, thyroid-stimulating hormone; WC, waist circumference; WHR, waist-to-hip ratio; WHtR, waist-to-height ratio.
biochemical indicators, there was no significant difference between the groups.

### Comparison of Cardiometabolic Risk Factors of the Study Groups

Significantly higher prevalences of hypertriglyceridemia and increased TG/HDL-c ratio were found in the group with IH (P = .029 and .047, respectively). In terms of other cardiometabolic risk factors, there was no significant difference between the groups (Table 2).

### Correlation of TSH Levels with Clinical and Biochemical Variables

The correlation analysis of TSH with clinical and biochemical characteristics in all individuals is shown in Table 3. Thyroid-stimulating hormone had a statistically significant positive relationship with TG, non-HDL-c, TC/HDL-c ratio, and TG/HDL-c ratio, as well as an inverse relationship with HDL-c (r = 0.217, P = .001; r = 0.160, P = .017; r = 0.170, P = .011; r = 0.218, P = .001; r = −0.138, P = .039, respectively). No correlation was determined between TSH and other parameters in the whole group. While TSH had a positive relationship with TG and TG/HDL-c ratio in both females (r = 0.188, P = .040 and r = 0.205, P = .024) and males (r = 0.256, P = .010 and r = 0.246, P = .013), TSH was found to have a positive relationship with non-HDL-c and TC/HDL-c ratio only in females (r = 0.181, P = .046 and r = 0.199, P = .028, respectively).

### Evaluation of Lipid Profiles According to Sex of the Patients

We also compared lipid profiles between children with obesity and with and without IH in different sex groups (Table 4). In the female subgroup, triglyceride/HDL-c ratio and the rates of hypertriglyceridemia were greater in children with IH compared to those with normal TSH (P = .04 and P = .03). Male children with IH had higher TG levels in comparison with males with normal TSH (P = .04).

### DISCUSSION

The long-term effects of high TSH in obesity are unknown. The possible effects of IH on cardiometabolic dimensions are still an important research topic. In the present study, the relationship between IH and cardiometabolic risk factors was evaluated in obese children and adolescents. The results demonstrated...
that elevated TSH levels were associated with adverse effects on lipid metabolism. Triglyceride, non-HDL-c, and the ratio of TG/HDL-c levels were found to be significantly higher in the IH group. In addition, hypertriglyceridemia and increased TG/HDL-c ratio were also found at a higher rate in this group. Furthermore, despite a positive correlation of TSH with TG levels, non-HDL-c, TG/HDL-c, and TC/HDL-c ratio levels, a negative correlation was found with HDL-c.

There are conflicting findings regarding the relationship between thyroid functions and BMI. Aside from studies that show the reverse, there are other studies that show a positive association between blood TSH levels and BMI.5,31 On the other hand, Giannakopoulos et al32 indicated that whereas BMI and association between blood TSH levels and BMI.5,31 On the other hand, Giannakopoulos et al32 indicated that whereas BMI and

![Table 3. Correlation of TSH levels with Clinical and Biochemical Variables](image)

| Variables          | TSH Level        |          |          |          |          |
|--------------------|------------------|----------|----------|----------|----------|
|                    | All Subjects     | Females  | Males    |          |          |
|                    | r     | P       | r     | P       | r     | P       |
| **Clinical characteristics** |       |          |          |          |          |
| Age (years)        | 0.007 | 0.914*  | 0.051 | 0.576*  | 0.073 | 0.456*  |
| Body weight (kg)   | −0.058 | 0.391* │ −0.064 | 0.484*  | −0.074 | 0.463*  |
| Body weight SDS    | −0.027 | 0.692*  | 0.018 | 0.842*  | −0.024 | 0.814*  |
| Body height (cm)   | −0.035 | 0.602*  | 0.004 | 0.967*  | −0.074 | 0.462*  |
| Body height SDS    | −0.024 | 0.726*  | −0.039 | 0.666*  | −0.021 | 0.836*  |
| BMI (kg/m²)        | −0.061 | 0.362*  | −0.043 | 0.635*  | −0.065 | 0.519*  |
| BMI SDS            | −0.045 | 0.502*  | 0.005 | 0.954*  | −0.024 | 0.809*  |
| BMI P              | −0.062 | 0.357*  | −0.051 | 0.575*  | −0.035 | 0.729*  |
| WC (cm)            | −0.029 | 0.691*  | −0.008 | 0.939*  | −0.040 | 0.719*  |
| HC (cm)            | −0.040 | 0.585*  | 0.045  | 0.654*  | −0.080 | 0.464*  |
| WHR                | 0.000  | 0.996*  | −0.074 | 0.456*  | 0.089  | 0.419*  |
| WHIR               | −0.015 | 0.842*  | −0.020 | 0.845*  | 0.027  | 0.809*  |
| SBP (mmHg)         | −0.094 | 0.173*  | −0.129 | 0.170*  | −0.067 | 0.516*  |
| DBP (mmHg)         | −0.095 | 0.171*  | −0.101 | 0.285*  | −0.039 | 0.709*  |

| **Biochemical characteristics** |       |          |          |          |          |
| tT3 (pg/mL)         | 0.023  | 0.749*  | −0.041 | 0.682*  | 0.079  | 0.466*  |
| tT4 (ng/dL)         | −0.026 | 0.700*  | −0.010 | 0.914*  | −0.020 | 0.845*  |
| Fasting glucose (mg/dL) | 0.113  | 0.119*  | 0.109  | 0.276*  | 0.086  | 0.424*  |
| Fasting insulin (µU/mL) | −0.027 | 0.694*  | −0.033 | 0.718*  | −0.033 | 0.745*  |
| HOMA-IR             | −0.015 | 0.822*  | −0.027 | 0.770*  | −0.033 | 0.743*  |
| TC (mg/dL)          | 0.106  | 0.114*  | 0.093  | 0.308*  | 0.136  | 0.175*  |
| TG (mg/dL)          | 0.217  | 0.001*  | 0.188  | 0.040*  | 0.256  | 0.010*  |
| LDL-c (mg/dL)       | 0.061  | 0.365*  | 0.094  | 0.305*  | 0.017  | 0.862*  |
| HDL-c (mg/dL)       | −0.138 | 0.039*  | −0.138 | 0.130*  | −0.099 | 0.325*  |
| Non-HDL-c           | 0.160  | 0.017*  | 0.181  | 0.046*  | 0.166  | 0.097*  |
| TC/HDL-c ratio      | 0.170  | 0.011*  | 0.199  | 0.028*  | 0.193  | 0.053*  |
| TG/HDL-c ratio      | 0.218  | 0.001*  | 0.205  | 0.024*  | 0.246  | 0.013*  |
| AST (IU/L)          | −0.106 | 0.113*  | −0.106 | 0.243*  | −0.105 | 0.294*  |
| ALT (IU/L)          | −0.046 | 0.498*  | −0.075 | 0.408*  | 0.004  | 0.967*  |

* Spearman correlation analyses.
* Pearson correlation analyses.
* r = −1.00, perfect negative correlation
* r = (−0.71−0.99), strong negative correlation
* r = (−0.30−0.70), moderate negative correlation
* r = (−0.01−0.29), weak negative correlation
* r = 0.00, no correlation
* r = 0.01−0.29, weak positive correlation
* r = 0.30−0.70, moderate positive correlation
* r = 0.71−0.99, strong positive correlation
* r = 1.00, perfect positive correlation

The bold P values are statistically significant.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; DBP, diastolic blood pressure; fT3, free T3; fT4, free T4; HC, hip circumference; HDL-c, high density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment of insulin resistance; LDL-c, low density lipoprotein cholesterol; P, percentile; SBP, systolic blood pressure; SDS, standard deviation score; TC, total cholesterol; TG, triglyceride; TSH, thyroid stimulating hormone; WC, waist circumference; WHR, waist to height ratio.
obtaining the leptin-mediated increase in TSH. In our study, there was no correlation between serum TSH levels and BMI. Perhaps this result can be explained by the fact that 88% of all our study groups consisted of pubertal children.

The effect of thyroid function on BP is complex and the mechanism is not well understood. Serum TSH levels in the upper reference range have been linked to hypertension in few studies.13-16 El-Adawy et al17 Cerbone et al18 and Yadav et al19 were unable to locate any significant difference in SBP and DBP in children with IH compared to euthyroid patients. The results of our study were similar to these 3 studies showing that the presence of IH did not affect BP levels compared to euthyroidism. Thyroid hormones are essential for glucose metabolism. Data on the possible effects of IH on IR in patients with childhood obesity are still debated and limited. There are studies supporting that hypothyroidism and SCH are associated with IR and also even fasting insulin and IR are positively linked with obesity.20-22 However, there was no difference in the presence of MetS between the groups with and without IH.

Thyroid hormones are important modulators of lipid metabolism. By boosting hepatic cholesterol production and reducing intestinal cholesterol absorption, they regulate lipid synthesis, metabolism, and mobilization.23 There are many studies investigating the relationship between IH and lipid profiles in obese children, but the results are conflicting. Here, we found that children and adolescents with obesity in the IH group had higher TG levels, non-HDL-c levels, and TG/HDL-c ratio, as well as higher rates of hypertriglyceridemia and a higher TG/HDL-c ratio. Therefore, our study results support that TSH, even within the normal range of serum concentrations, can adversely influence lipid metabolism. A prior cross-sectional research on German children and adolescents found a link between higher TSH levels and less favorable lipid levels.24 Increased blood TSH levels, while remaining within the normal range, were found to be favorably connected with total cholesterol, LDL-c, and TG, but negatively correlated with HDL-c in a population-based study involving 30 656 participants.25 Yadav et al26 reported higher LDL-c, TG, TG/HDL-c ratio and lower HDL-c levels in children with SCH compared to euthyroid subjects. The TG level was observed to be greater in the increased TSH group in Kara’s study,27 except for TG levels, Shalitin et al28 found no significant differences in lipid profiles between individuals with IH. In Cerbone et al’s study, HDL-c levels were shown to be decreased in SCH patients.29 In Kara’s study, the SCH group’s HDL-c level was shown to be lower than the control group’s level.30 We identified a substantial negative association between TSH levels and HDL-c in our study, despite the fact that there was no significant difference in HDL-c between

Table 4. Evaluation of Lipid Profiles According to Sex of the Patients

| Variables                        | Females (n = 123) | Males (n = 101) |
|----------------------------------|-------------------|-----------------|
|                                  | With Isolated     | With Normal     | P          | With Isolated     | With Normal     |
|                                  | Hyperthyrotropinemia | Thyroid Function |          | Hyperthyrotropinemia | Thyroid Function |
| TC (mg/dL)                       | 160.7 ± 34.2      | 156.8 ± 30.5    | .51c      | 166.2 ± 28.2      | 160.4 ± 30.9    | .33a          |
| TG (mg/dL)                       | 116 (51-344)      | 91.7 (35-265)   | .07b      | 118 (44.7-301)    | 93.4 (40-335)   | .04b          |
| LDL-c (mg/dL)                    | 86.6 (28.4-157)   | 85.7 (34.8-208) | .64c      | 90.7 (42-154)     | 89.7 (21.5-178) | .88b          |
| HDL-c (mg/dL)                    | 43.8 (27.8-82)    | 45.3 (32.7-90.8)| .20b      | 46.4 ± 12.8       | 47.3 ± 11.6    | .67a          |
| Non-HDL-c                        | 116.6 (55.8-189.7)| 103.9 (42.6-235.1)| .11b | 119.8 ± 28.8       | 112.9 ± 33.4    | .28a          |
| TC/HDL-c ratio                   | 3.46 (2.13-6.08)  | 3.26 (1.8-6.95) | .09a      | 3.8 ± 1.12        | 3.37 ± 1.05    | .29a          |
| TG/HDL-c ratio                   | 2.61 (0.91-13.76) | 2.08 (0.63-6.83)| .04b      | 2.5 (0.56-10.65)  | 2.22 (0.51-6.08)| .08b          |
| Hypertriglyceridemia             | 18 (32.1%)        | 10 (15.6%)      | .03c      | 12 (28.6%)        | 12 (20.7%)     | .36c          |
| Decreased HDL-c                  | 21 (36.8%)        | 14 (21.9%)      | .07c      | 14 (33.3%)        | 17 (28.8%)     | .62c          |
| Increased TC                     | 8 (14%)           | 6 (9.4%)        | .42c      | 8 (19%)           | 6 (10.2%)      | .20c          |
| Increased LDL-c                  | 5 (8.9%)          | 4 (6.2%)        | .73a      | 3 (7.1%)          | 7 (11.9%)      | .51a          |
| Increased nonHDL-c               | 8 (14%)           | 5 (7.8%)        | .27c      | 8 (19%)           | 11 (16.8%)     | .95c          |
| Increased TC/HDL-c ratio         | 5 (8.8%)          | 5 (7.8%)        | .84c      | 6 (14.3%)         | 8 (13.6%)      | .92c          |
| Increased TG/HDL-c ratio         | 22 (38.6%)        | 16 (25%)        | .10c      | 17 (40.5%)        | 17 (28.8%)     | .22c          |

*Student’s t-test; Data are given as mean ± SD.  
*Mann-Whitney U test; Data are given as median (minimum-maximum).  
*Pearson chi-square test.  
*Fisher’s exact test.  
The bold *P* values are statistically significant.  
HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.
Thyroid hormones have a critical role in cardiovascular hemodynamics. Although TSH levels are within the normal range, children with obesity and IH may still be at risk for cardiovascular disease in the future because of abnormalities in their lipid profiles. In our IH patients, higher ARR was detected compared to the euthyroid group. Similar to our findings, Cerbone et al. documented an increased plasma TG/HDL-c ratio in patients with SCH, indicating an atherogenic risk profile. Akici et al. reported that in the presence of SCH, the percentage of atherogenic index (AIP, log [TG/HDL-c]) increased 2.4 times without any change in CRR. Although in terms of CRR, there was no significant difference between the groups with and without IH, we found that both ARR and CRR were positively associated with increased TSH levels. To our findings, increased children’s non-HDL-c and TG/HDL-c ratios with obesity and IH, as well as positive correlation of TSH with non-HDL-c, TG/HDL-c ratio, and TC/ HDL-c ratio, likely have a potential risk of development for atherosclerotic disease which has been demonstrated Heart and Pathobiological Determinants of Atherosclerosis in Youth Study in Bogalusa.

There are very few reports on sex differences in the relationship between thyroid function and lipid profile. Akici et al. made further analysis by sex and showed that SCH increased the risk of AIP and CRR in females by about 2 times compared to males. In our study, we found that TG and ARR were positively correlated with TSH in both females and males, additionally, in females, CRR and non-HDL-c were similarly favorably linked with TSH only. Furthermore, compared with normal thyroid function groups by sexes, ARR and percentage of hypertriglyceridemia were higher in females with IH, while males with IH had greater TG levels. These findings recommend that females are affected much more than males in terms of the lipid profile if IH is present. In a research evaluating children with obesity in Japan, TSH levels were positively connected with non-HDL-c levels in females but not in men, similar to our study. Minami et al. reported positive correlations of TSH with non-HDL-c in only girls. However, in contrast to our study, in the lbabal et al’s study, compared to those with normal TSH, males with moderate SCH had greater levels of TC and non-HDL-c. These findings imply that sex influences the association between TSH and lipids, and that sex differences are linked to race/ethnicity, age, pubertal stage, and obesity severity.

Study Limitations
There are some drawbacks of this study. Firstly, this study is retrospective in nature and has a small sample size. Secondly, while our findings indicate a link between IH and dyslipidemia, they do not imply causation. In order to establish the causality, studies showing the improvement in lipid parameters after normalization of TSH are needed. Thirdly, TSH levels are affected by laboratory technique and time of blood sample collection, controls were not taken since it is not clinically significant. Since the study was retrospective, study groups were formed according to a single measurement value. Lack of racial and cultural variety, as well as information on relevant variables that can affect lipid levels, such as dietary habits, physical activity, and family history of hyperlipidemia, are all drawbacks.

CONCLUSION

In conclusion, the current study compared obese children and adolescents with children and adolescents of similar age and BMI and suggested that IH is associated with the deterioration of lipid metabolism, especially in females. Since dyslipidemia is accepted as a risk factor for cardiovascular diseases, IH might negatively influence cardiovascular function in children and adolescents with obesity. To test this idea and investigate whether LT4 supplementation is beneficial in improving dyslipidemia and preventing the development of cardiovascular risks in hyperthyrotropinemic children and adolescents with obesity having abnormal lipid profiles, prospective clinical studies with bigger sample sizes and longer follow-up periods are required.

Ethics Committee Approval: This study was approved by the Ethics Committee of Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital (Approval No: 2018/18-08).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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