Invest Clin 63(2): 126 - 136, 2022 https://doi.org/10.54817/IC.v63n2a02

Evaluation of thyroid function and metabolic parameters in obese and overweight children: A prospective case-control study.

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Key words: body mass index; insulin; metabolic parameters; obesity; thyroid hormone.

Abstract. Obesity is considered an important global public health challenge, and its prevalence is rapidly increasing in children. We investigated in this study if the upper-normal TSH level may be associated with metabolic syndrome parameters, including obesity, high blood pressure, and dyslipidemia and changes in insulin sensitivity in overweight and obese children. We also investigated whether there is a relationship between BMI and these parameters. This prospective case-control study comprised 145 participants (74 females, 71 males) aged 5–18 years. Participants were divided into three groups according to their BMI z-score, as overweight, obese and control. The control group included 35 age and sex-matched healthy subjects. Thyroid stimulating hormone levels of control, overweight and obese groups were 2.14 ± 1.27, 2.97 ± 1.26 and 3.13 ± 1.11, respectively ($p<0.05$). There was a significant positive correlation between TSH and the BMI, BMI z-scores between overweight and obese groups ($r=0.302$, $p=0.000$), ($r=0.121$, $p=0.004$), respectively. The current study suggests that increased serum TSH levels, even within the normal range, in overweight and obese children is associated with the impairment of metabolic parameters, including dyslipidemia and insulin sensitivity. For that reason, TSH levels in the high-normal range should be considered as a risk factor for metabolic syndrome and its components.

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Evaluación de la función tiroidea y los parámetros metabólicos en niños obesos y con sobrepeso: Un estudio prospectivo de casos y controles.

Invest Clin 2022; 63 (2): 126 – 136

Palabras clave: índice de masa corporal; insulina; parámetros metabólicos; obesidad; hormona tiroidea.

Resumen. La obesidad se considera un importante desafío de salud pública mundial y su prevalencia está aumentando rápidamente en los niños. En este estudio, se investigó si el nivel normal superior de TSH puede estar asociado con los parámetros del síndrome metabólico, incluida la obesidad, la presión arterial elevada, cambios en los lípidos y la sensibilidad a la insulina, en niños con sobrepeso y obesidad. También investigamos si existe una relación entre el IMC y estos parámetros. En este estudio prospectivo de casos y controles se incluyeron a 145 participantes (74 hembras, 71 varones) de entre 5 y 18 años. Los participantes se dividieron en 3 grupos según el puntaje z del IMC, como sobrepeso, obesidad y control. El grupo de control incluyó 35 sujetos sanos emparejados por edad y sexo. Los niveles de hormona estimulante de la tiroides de los grupos de control, con sobrepeso y obesos fueron 2,14 ± 1,27, 2,97 ± 1,26 y 3,13 ± 1,11, respectivamente (p <0,05). Hubo una correlación positiva significativa entre la TSH y el BMI, la puntuación z del IMC entre los grupos con sobrepeso y obesidad (r = 0,302, p = 0,000), (r = 0,121, p = 0,004), respectivamente. Por esa razón, el nivel de TSH en el rango normal alto debe considerarse como un factor de riesgo del síndrome metabólico y sus componentes.

Received: 08-09-2021 Accepted: 08-12-2021

INTRODUCTION

Obesity is considered an important global public health challenge, and its prevalence is rapidly increasing in children [1,2]. Obesity is defined as a body mass index (BMI) ≥ 95th percentile for children of the same age and gender [3]. It is believed that obese individuals are at an increased risk of metabolic syndrome and thyroid dysfunction [4,5].

There is a wide variation in reference values for thyroid stimulating hormone levels (TSH) in children [6]. Many laboratories use values of about 4.5 to 5.0 μIU/mL as the upper-normal range for TSH, and some experts suggest that the upper-normal TSH level in children should be lowered due to the risk of obesity, dyslipidemia, and changes in blood pressure (BP) and insulin sensitivity [7-10].

Thyroid hormone has a key role in regulating metabolism. It is well known that overt hypothyroidism may cause obesity in individuals; however, there is no clarity regarding subclinical hypothyroidism [11]. Subclinical hypothyroidism is defined biochemically as a normal serum free thyroxine level (FT4) concentration in the presence of an elevated serum TSH concentration [11]. Thyroid hormone regulates both basal metabolism and thermogenesis [12,13]. Moreover, it is involved in glucose and fat metabolism [12]. Because of these interactions between thy-

roid hormones and metabolic parameters, there is an increasing doubt of whether even mild thyroid dysfunction may induce obesity in children [14,15].

We speculated in this study that the upper-normal TSH level may be associated with metabolic syndrome parameters, including obesity, blood pressure, lipid and insulin sensitivity in overweight and obese children. We also investigated whether there is a relationship between BMI and these parameters.

MATERIALS AND METHODS

Study population

This prospective case-control study comprised 145 participants (74 females, 71 males) aged 5–18 years, and it was conducted in an ethnically homogeneous population between 2012 and 2015. Participants were divided into three groups according to their BMI z-score, as overweight (n=64), obese (n=46) and control. The control group included 35 age and sex-matched healthy subjects. Written informed consent and assent were obtained from participants and parents. Ethics approval was obtained from the Local Ethics Committee (protocol number/date:9204/09.04.-12) for this research, and the study was managed in accordance with the Declaration of Helsinki. Children with any known disease (any thyroid disease, cardiovascular disease, etc.) or using any pharmacologic treatment known to affect BMI z-score, thyroid hormones, blood pressure, lipid and glucose metabolism were excluded from the study.

Anthropometric measurements

Standing height (SH), body weight (BW), blood pressure measurement, waist and hip circumferences were obtained from all participants and made according to the World Health Organization recommendations [16]. Blood pressure was measured in the sitting position after five minutes of rest in a quiet environment with a mechanical sphygmomanometer. Blood pressure was measured twice and the average of the measurements was used as the final value. Standing height was measured with a Harpenden stadiometer, and participants were weighed in lightweight clothing. Body mass index was calculated as body weight in kilograms divided by the square of standing height in meters (BMI= kg/m^2). We used BMI z-scores to compare BMI values across different ages and by gender. Overweight was defined as $+1 <$ BMI z-score $\leq +2$ SDs, and obesity was defined as a BMI z-score over 2 SDs from the mean of natioanal charts [17].

Laboratory studies

The blood samples were obtained after an 8-12-hour overnight fast for analysis of the lipid profile, fasting plasma glucose (FPG), fasting insulin (FI), TSH and FT4. Total cholesterol (TC), high density lipoprotein cholesterol (HDL-C) and triglyceride (TG) levels were measured by an enzymatic colorimetric assay (Roche Cobas İntegra® 800, Mannheim, Germany). Low density lipoprotein cholesterol (LDL-C) was calculated for samples containing TG <400 mg/dL using the Friedewald formula. Fasting plasma glucose was measured by the hexokinase method (Roche Cobas İntegra® 800, Mannheim, Germany). Fasting Insulin, TSH and FT4 were measured by the electrochemiluminescence immunoassay method (The ADVIA Centaur® CP Immunoassay System, Erlangen, Germany). The reference values of TSH and FT4 in our center are 0.38-4.5 μIU/mL and 0.58-1.38 ng/dL, respectively. Insulin resistance was estimated by the homeostatic model [Homeostasis model assessment of insulin resistance (HOMA-IR) = fasting plasma glucose x fasting insulin /405] [9].

Statistical analysis

The data were evaluated using the Statistical Package for Social Sciences 21.0 program for Windows. Continuous variables were calculated as mean+standard

deviation. The normality of the distribution of continuous variables was confirmed by the Kolmogorov-Smirnov test. A one-way analysis of variance tests was used to evaluate comparisons between the groups. Pearson correlation analysis was used to evaluate the relationships. A p-value <0.05 was accepted as statistically significant.

The sample size estimation of the study was calculated by using G*Power 3.1.9.4 (with 90% power and 5% type I error rates).

RESULTS

The study included 110 overweight and obese participants and 35 healthy controls. The male/female ratio of overweight and obese groups was 31/33 and 22/24, respectively, while it was 18/17 for the control group (p >0.05). Mean age of control, overweight and obese groups were 9.7 ± 3.6; 10.3 ± 2.6; 10.8 ± 2.7 years, respectively (p >0.05). The anthropometric and laboratory characteristics of all participants are summarized in Table 1.

Table 1
Anthropometric and laboratory characteristics of the study participants.

Parameters	Control group (n=35)	Overweight group (n=64)	Obese group (n=46)	p
	Mean ± SD			
Age, yr	9.7 ± 3.6	10.3 ± 2.6	10.8 ± 2.7	0.12
Gender (M/F), (n,%)	18 (51.4)/17 (48.5)	31 (48.4)/33 (51.5)	22(47.8)/24 (52.1)	0.64
BMI (kg/m²)	20.94 ± 2.46	27.26 ± 1.29	32.98 ± 2.87	**<0.01**
BMI-Z score	0.63 ± 0.15	1.59 ± 0.48	2.47 ± 0.36	**<0.01**
WHR (cm/cm)	0.74 ± 0.03	0.82 ± 0.06	0.87 ± 0.07	**<0.01**
SBP (mmHg	106.6 ± 9.3	107.8 ± 12.2	110.3 ± 10.6	0.22
DBP (mmHg)	69.2 ± 5.9	69.1 ± 7.1	73.5 ± 9	0.13
TC (mg/dL)	156.1 ± 15.8	169.3 ± 38.3	171.93 ± 35.8	**<0.01**
TG (mg/dL)	89.6 ± 22.5	97.2 ± 49.3	101.8 ± 37	**<0.01**
LDL – C (mg/dL)	92 ± 14.5	97.4 ± 30	105.3 ± 31.6	**0.01**
HDL– C (mg/dL)	46.9 ± 10.3	48 ± 11.7	47.7 ± 12.9	0.90
FPG (mg/dL)	78.9 ± 12.7	89.6 ± 5.6	101.9 ± 6.2	**0.03**
Insulin (μU/mL)	13.32 ± 7.35	15.14 ± 6.32	21.69 ± 10.99	**<0.01**
HOMA-IR	1.12 ± 1.79	2.05 ± 1.45	2.44 ± 2.54	**<0.01**
TSH (μIU/mL)	2.14 ± 1.27	2.97 ± 1.26	3.13 ± 1.11	**<0.01**
FT4 (ng/dL)	1.21 ± 0.18	1.23 ± 0.14	1.18 ± 0.19	0.23

BMI, body mass index; WHR, waist-to-hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglycerides; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment of insulin resistance; TSH, thyroid-stimulating hormone; FT4, free thyroxine.

Thyroid stimulating hormone levels of the control, overweight and obese groups were 2.14 ± 1.27, 2.97 ± 1.26 and 3.13 ± 1.11, respectively ($p<0.05$), and the FT4 levels of control, overweight and obese subjects was 1.21 ± 0.18, 1.23 ± 0.14 and 1.18 ± 0.19, respectively ($p >0.05$). TSH levels were found to be slightly high in 13.6% (15 out of 110 subjects) of overweight and obese groups. There was a significant positive correlation between TSH and BMI, BMI z-scores between the overweight and obese groups ($r=0.302$, $p=0.000$), ($r=0.121$, $p=0.004$), respectively. Additionally, FT4 and BMI, BMI z-score between the overweight and obese groups ($r=-0.042$, $p=0.009$), ($r=-0.023$, $p=0.011$), respectively. Correlation between thyroid hormones and metabolic parameters in overweight and obese participants were summarized in Table 2.

Table 2
Correlation between thyroid hormones and metabolic parameters in overweight and obese subjects.

Parameters	TSH		FT4	
	r	p	r	p
Age	-0.023	**0.000**	0.010	0.231
BMI	0.302	**0.000**	-0.042	**0.009**
BMI-Z score	0.121	**0.004**	-0.023	**0.011**
WHR	0.130	**0.010**	-0.025	**0.018**
SBP	0.231	**0.006**	0.173	**0.014**
DBP	0.181	**0.023**	0.052	**0.031**
TC	0.227	**0.019**	-0.143	0.056
TG	0.021	**0.010**	-0.041	0.072
LDL – C	0.125	**0.016**	-0.055	0.133
HDL– C	0.031	0.235	-0.012	0.151
FPG	0.011	**0.018**	-0.013	0.068
Insulin	0.035	**0.044**	-0.019	0.124
HOMA-IR	0.023	**0.032**	-0.011	0.221

The overweight and obese groups had higher TC, LDL-C and TG levels than the control group ($p<0.05$), however, HDL-C level was significantly different between groups ($p >0.05$). We found a significant positive correlation between TSH and TC, LDL-C, TG ($r=0.227$, $p=0.019$), ($r=0.125$, $p=0.016$) and ($r=0.021$, $p=0.010$), respectively, but not with HDL-C ($r=0.031$, $p=0.235$).

Fasting plasma glucose, insulin and HOMA-IR values were significantly different among groups ($p <0.05$), (Table 1) and we found a significant positive correlation between TSH and FPG, insulin, HOMA-IR ($r=0.011$, $p=0.018$), ($r=0.035$, $p=0.044$), ($r=0.023$, $p=0.032$), respectively. However, there was not a significant correlation between FT4 and FPG, insulin, HOMA-IR ($r=-0.013$, $p=0.068$), ($r=-0.019$, $p=0.124$), ($r=-0.011$, $p=0.221$), respectively.

The correlation between thyroid hormones (TSH and FT4) and BMI, HOMA-IR in overweight and obese children can be seen in Fig. 1.

The anthropometric and laboratory characteristics of overweight and obese groups according to the gender and age are summarized in Tables 3 and 4.

DISCUSSION

Obesity is a critical public health problem associated with many chronic disorders, including metabolic syndrome and thyroid dysfunction [18,19]. The most common thyroid dysfunction is hyperthyrotropinemia, which is believed to be an adaptive process to excess body mass, energy expenditure and thermogenesis [3,20]. In the present study, we found a significant association and correlation between TSH and BMI, BMI z-scores in overweight and obese children. Thyroid stimulating hormone levels in these groups were higher than in the healthy control group. FT4 had a significant negative correlation with BMI, BMI z-scores, however, not a significant association. These findings are consistent with previous studies [16,21,22].

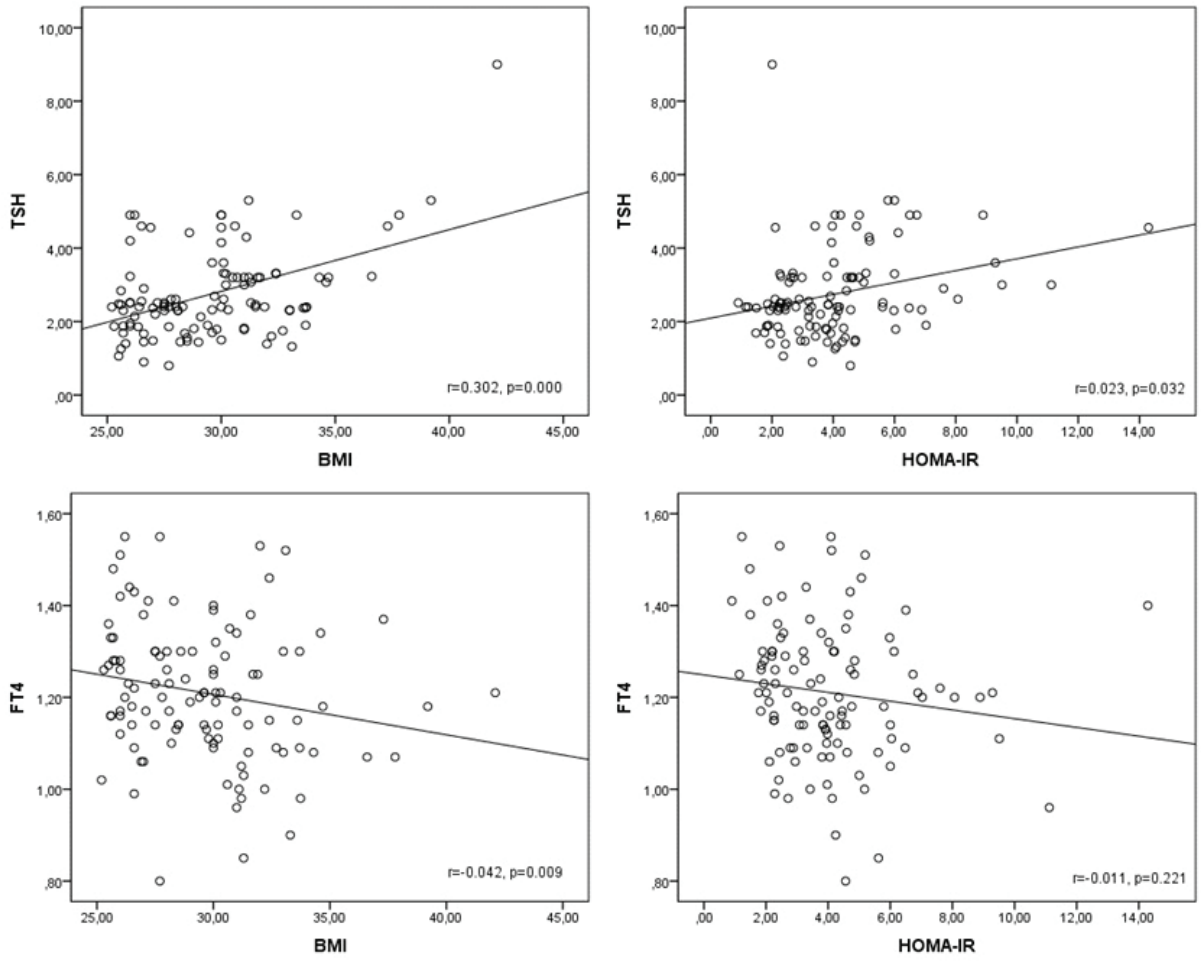

Fig. 1. Correlation between thyroid hormones (TSH and FT4) and BMI, HOMA-IR in overweight and obese children.

The mechanisms of the association between TSH and obesity is not definitely understood. However, several mechanisms have been proposed to explain this complex relationship, including derangement of the hypothalamic–pituitary axis, thyroid hormone resistance, changes in the activity of deiodinases, the impact of leptin and chronic low grade inflammation, etc. [23,24].

According to recent studies, the prevalence of isolated hyperthyrotropinemia in overweight and obese children is thought to be between 15% and 23% [25,26]. However, in our study, it was found to be only 15 out of 110 children (13.6%). The case selection and study design may be the reason for this discrepancy.

Classically, obesity-associated dyslipidemia is a well-known condition, and characterized by elevated TC, LDL-C, TG and decreased HDL-C level, and has been described both in overt and subclinical hypothyroidism [27,28]. Consistent with this, we found that TC, LDL-C and TG levels were higher in the overweight and obese groups than in the control group. However, the HDL-C level was significantly different between groups. That was confirmed in another study conducted by Aeberli *et al.* [24]. Additionally, we found a significant positive correlation between TSH

Table 3
Anthropometric and laboratory characteristics of overweight and obese groups according to the gender.

Parameters	Male	Female	p
	Mean ± SD		
Gender, n, (%)	53 (48.2)	57 (51.8)	-
Age, yr	10.2 ± 2.8	11.3 ± 3.3	0.09
BMI (kg/m^2)	29.36 ± 3.42	29.83 ± 3.59	0.50
BMI-Z score	2.01 ± 0.54	2.18 ± 0.46	0.16
WHR (cm/cm)	0.87 ± 0.05	0.84 ± 0.07	0.23
SBP (mmHg	108.5 ± 12.1	111.9 ± 12.7	0.89
DBP (mmHg)	71.1 ± 7.9	70.8 ± 8.4	0.85
TC (mg/dL)	167.5 ± 36.3	164.6 ± 37.2	0.10
TG (mg/dL)	99.9 ± 45.6	98.7 ± 44.1	0.88
LDL – C (mg/dL)	102.7 ± 31.6	98 ± 30.2	0.08
HDL– C (mg/dL)	47.7 ± 12.9	48 ± 11.8	0.93
FPG (mg/dL)	96.1 ± 6.7	94.2 ± 8.5	0.41
Insulin (μU/mL)	16.78 ± 8.48	19.12 ± 9.35	0.06
HOMA-IR	2.16 ± 1.96	2.28 ± 2.18	0.08
TSH (μIU/mL)	2.99 ± 1.08	3.09 ± 1.28	0.66
FT4 (ng/dL)	1.22 ± 0.17	1.19 ± 0.13	0.31

BMI, body mass index; WHR, waist-to-hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglycerides; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment of insulin resistance; TSH, thyroid-stimulating hormone; FT4, free thyroxine.

and TC, LDL-C, TG, and similar observations were reported by Le *et al.* and Canaris *et al.*[9,29]. In contrast to these findings, a retrospective analysis of a large community-based pediatric population in Rochester, which was conducted by Nader *et al.*, found only a significant positive correlations between TSH and TG [30]. These differences may be due to the sample size and diverse characteristics of the study participants.

The relationship between thyroid hormonal derangement and glucose metabolism in obesity is a complex interdependent interaction [31,32]. Recently, the study performed by Ambrosi *et al.* in Milan shown that TSH had a significant positive correlation with fasting insulin and HOMA-IR in 581 obese patients[33]. Similar results were reported by Reinehr *et al.*, and our findings were also in line with these studies [26]. However, in contrast to these findings, this association was not shown in some other studies [34,35].

In our study, metabolic parameters and blood pressure values were also compared between overweight and obese patient groups on the basis of age and gender. However, we did not find a significant association. These findings are consistent with previous studies [21,36,37].

The main strength of this study is that it was conducted prospectively in a healthy control group and in an ethnically homogeneous population. The limitations of the study include the relatively small sample size, a lack of evaluation of free triiodothyronine, thyroxine-binding globulin and thyroid peroxidase.

Table 4
Anthropometric and laboratory characteristics of overweight and obese groups according to the age.

Parameters	<11 years	≥11 years	p
	Mean ± SD		
Male/Female, n, (%)	22 (39.3) / 34 (60.7)	19 (35.2) / 35 (64.8)	0.40
Age, yr	8.39 ± 1.7	13.5 ± 1.9	**0.02**
BMI (kg/m²)	28.73 ± 2.31	30.64 ± 3.47	0.14
BMI-Z score	2.05 ± 0.57	2.24 ± 0.3	0.21
WHR (cm/cm)	0.83 ± 0.05	0.85 ± 0.07	0.12
SBP (mmHg	108.9 ± 12.8	112.8 ± 9.9	0.31
DBP (mmHg)	69.4 ± 7.1	70.5 ± 8.6	0.42
TC (mg/dL)	168.5 ± 39.1	169.6 ± 35.4	0.87
TG (mg/dL)	98 ± 44.9	104.4 ± 43.8	0.22
LDL – C (mg/dL)	103.6 ± 32.9	100 ± 29.2	0.58
HDL– C (mg/dL)	47.7 ± 10.9	48.1 ± 13.4	0.85
FPG (mg/dL)	91 ± 5.4	95 ± 6.5	0.39
Insulin (μU/mL)	17.88 ± 5.89	19.98 ± 10.79	0.22
HOMA-IR	2.35 ± 1.39	2.27 ± 2.51	0.34
TSH (μIU/mL)	2.94 ± 1.03	2.81 ± 1.37	0.87
FT4 (ng/dL)	1.22 ± 0.15	1.19 ± 0.13	0.22

BMI, body mass index; WHR, waist-to-hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglycerides; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment of insulin resistance; TSH, thyroid-stimulating hormoneL; FT4, free thyroxine.

The most important finding of this study is that increasing serum TSH level, even within the upper-normal level, in overweight and obese children can be associated with the impairment of metabolic parameters, including dyslipidemia and insulin sensitivity. Although the mechanism underlying this condition has not been fully elucidated yet, it is maybe an early sign of hypothyroidism, an autoimmune thyroid disease, or it may result from derangement of the hypothalamic–pituitary axis, the impact of leptin and chronic low grade inflammation, etc. [23,24,38,39].

As a result, the upper-normal serum TSH level should be considered as a risk factor of metabolic syndrome and its components in overweight and obese children, and this condition should be taken into account by researchers.

Funding

None.

Ethical approval

Given by Ethics Committee of Zeynep Kamil Maternity and Children's Health and Diseases Training and Research Hospital Ethics Committee (9204/09.04.2012).

Conflict of Interest

None.

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Author contributions

All authors made a significant contribution (concept and design of the study, acquisition of data, analysis and interpretation of the data, drafting or critically reviewing the manuscript, and final approval of the version of the article) to this article.

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