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The prevalence of subclinical hypothyroidism in obese children and adolescents and its effects on metabolic parameters

Obez çocuk ve adolesanlarda subklinik hipotiroidi sıklığı ve metabolik parametreler üzerine olan etkileri

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SUMMARY

Objective: To compare cardiovascular risk factors in obese patients with or without Subclinical Hypothyroidism (SH), also to estimate the prevalence of SH in obese children and adolescents.
Method: A total of 226 obese children and adolescents aged 6-18 years were included in the study. Two groups were created as euthyroid group (n=195) and SH group (n=31). After an 8-12 hour overnight fasting, serum blood glucose, insulin, HDL, LDL, cholesterol, triglyceride TSH, free T4, ALT, AST levels were measured. HOMA-IR and atherogenic index (AI) were calculated.
Results: Prevalence of SH was estimated as 14.1 %. The values of fasting glucose, fasting insülin, ALT, AST, TSH, HOMA-IR levels were significantly higher ın SH group than euthyroid group. There was a positive correlation between TSH and fasting glucose, insülin, triglyceride, ALT, AST, HOMA-IR, AI. It was also demonstrated that the TSH level was significantly and independently related to HOMA-IR value ın multiple regression analysis (p=0.001).
Conclusions: Obese patients with SH may be more susceptible to metabolic complications than euthyroid subjects.
Keywords: Adolescent, child, obesity, prevalence, subclinical hypothyroidism

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ÖZET

Amaç: Subklinik Hipotiroidi(SH)'si olan ve olmayan obezlerde kardiyovasküler risk faktörlerini karşılaştırmak ve obez çocuk ve adolesanlarda SH sıklığını hesaplamak
Yöntem: Çalışmaya yaşları 6-18 arası değişen 226 obez çocuk ve adolesan alındı. Ötiroid grup (n=195) ve SH grup (n=31) olmak üzere 2 grup oluşturuldu. 8-12 saatlik açlığı takiben, kan şekeri, insülin, HDL, LDL, kolesterol, trigliserit, TSH, serbest T4, ALT, AST düzeyleri ölçüldü. HOMA-IR ve Aterojenik İndeks (AI) hesaplandı.
Bulgular: Subklinik Hipotiroidi sıklığı %14,1 olarak hesaplandı. Açlık kan şekeri, insülin ALT, AST, TSH ve HOMA-IR düzeyleri SH grupta ötiroid grupla karşılaştırıldığında istatistiksel olarak anlamlı düzeyde daha yüksekti. TSH düzeyi ile açlık kan şekeri, insülin, trigliserit ALT, AST, HOMA-IR ve AI arasında pozitif bir korelasyon vardı. Ayrıca multipl regresyon analizi yapıldığında TSH düzeyinin HOMA-IR ile anlamlı düzeyde ilişkili olduğu görüldü (p=0.001).
Sonuç: Subklinik hipotiroidisi olan obez çocuk ve adolesanlar ötiroid grupla karşılaştırıldığında metabolic komplikasyonlara daha yatkındır.
Anahtar sözcükler: Adolesan, çocuk, obezite, prevalans, subklinik hipotiroidi

INTRODUCTION

Subclinical hypothyroidism (SH) is defined as elevated serum thyroid stimulating hormone (TSH) in the presence of normal serum total and free thyroxine (fT4) levels[1]. The prevalence of SH is 4-20% in adults, and 1.5-3% in children[2]. There are several factors associated with SH such as Hashimoto's thyroiditis, iodine deficiency, medications, gene defects, genetic syndromes, and obesity, etc.

It is well documented that overt hypothyroidism related metabolic abnormalities such as coroner artery disease, insülin resistance and dyslipidemia[3-5]. The role of hypothyroxinemia in cardiovascular diseases may be explained by thyroid hormone receptors present both myocardial and endothelial tissues[6]. On the other hand decreased thyroid hormone levels is associated with dyslipidemia that is related to coroner artery diseases. So overt hypothyroxinemia is related with cardiovascular disease.as an initiating or exacerbating factor. However, there is a limited study with inconsistent findings regarding SH and the presence of metabolic abnormalities[6-8].

Obesity is one of the well-known risk factors related to SH as a cause or consequence of it. The prevalence of SH among obese children was estimated as 10-23%[9;10]. Despite the unclarity, the potential underlying mechanism of SH in children with obesity, some possible explanation provided in the literature; an adaptation process for increasing energy expenditure, a functional disorder in the hypothalamic-pituitary-thyroid axis, resistance to thyroid hormones, increased leptin related production of thyroid releasing hormone[2;9].

Both obesity and hypothyroidism is related to increased cardiovascular risk. Thereby, early recognition of cardiovascular risk in patients with obesity and SH has become more critical. The aim of the study was to compare cardiovascular risk factors in obese patients with or without SH, also to estimated the prevalence of SH in obese children and adolescents.

MATERIAL AND METHODS

This study was performed in the Pediatric Endocrinology Department of Cumhuriyet University Hospital. Two hundred sixty-three obese children 6-18 years of age who had been brought to the outpatient clinic were consecutively recruited for the study from September 2017 to November 2018. The exclusion criteria were a history of chronic disorders, hypertension, use of thyroid hormone or any medications, patients with familial cardiovascular risk factors, autoimmune thyroid diseases or ıodine deficiency, secondary obesity, and TSH level higher than 10 IU/mL. After exclusion of 37 patient, 219 subjects were divided into two groups according to TSH levels; Euthyroid group (n=195) and subclinical hypothyroid group (n=31). The institutional Ethics Committee approved the study protocol.

All patients weights were determined using a calibrated digital scale, and their heights were measured in triplicate to the nearest millimeter using a calibrated stadiometer. Blood pressure was measured with a sphygmomanometer cuff suitable for the subject's arm circumference while the subject was seated. Blood pressure readings were taken twice, 2 min apart, and the average measurement was recorded. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m^2). Obesity was defined, according to the BMI percentiles for the Turkish population based on gender and age, as being≥95th percentile[11].

Venous blood samples were obtained from all of the patients from the antecubital region between 8.00 and 8.30 am after an 8-12 hour overnight fast. The serum sample tubes were allowed to clot before centrifugation. After centrifugation at 4°C for 15 minutes at 3500 rpm, serum insulin, HDL, LDL, cholesterol, triglyceride TSH, free T4 levels were determined with the electrochemiluminescent immunoassay (Roche Cobas e601, Germany). Serum blood glucose, serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST)concentrations were measured colorimetric method (Mindray BS 2000, China).

Subclinical hypothyroidism was defined as elevated serum TSH levels (4.5-10.0 mIU/L) in the presence of normal serum concentrations of free thyroxine level. We assessed insulin sensitivity using the homeostasis model of insulin resistance (HOMA-IR) index as a surrogate marker for insülin resistance. HOMA-IR values were calculated using the following formula: [fasting insulin level (μU/mL) multiplied by fasting glucose level (mg/dL) and divided by 405][12]. The atherogenic index of plasma (AI) was calculated the logarithm of the molar ratio of triglyceride to high-density lipoprotein cholesterol (TG/HDL-C)[13].

RESULTS

Prevalence of SH was estimated as 14.1 %. The mean ages of euthyroid and subclinical hypothyroid groups were similar (12.03±3.1 and 12.09±2.5 years, respectively, p = 0.92). The groups were also similar according to their sex and pubertal status (p= 0.33 and p=0.99, respectively). The values of fasting glucose, fasting insülin, ALT, AST, TSH, HOMA-IR levels were significantly higher in SH group than euthyroid group, whereas weight-SDS, height SDS, BMI-SDS, systolic and diastolic BP, triglyceride, HDL, LDL, fT4 and AI were similar (p>0.05). The baseline metabolic and anthropometric characteristics of the study population have been presented in Table 1.

Table 1: Baseline metabolic and anthropometric characteristics of the study population

	SH Group (n=31)	**Euthyroid Group** (n=195)	**p**
Age, years	12.09±2.5	12.03±3.1	0.92
Gender (% Girls)	61.3	51.3	0.33
Weight Z-score	2.48±1.08	2.51. ±1.02	1.08
Height Z-score	0.53±0.97	0,62±1.03	0.87
BMI Z-score	2.35±0.76	2.34±0.73	0.89
Prepuberty (%)	35,5	36.9	0.99
SBP (mm-Hg)	119.7±17.5	116.8±14.8	0.39
DBP (mm-Hg)	80±14.7	76.3±14.2	0.16
Fasting glucose (mg/dL)	85.9±6.7	82.8±6.0	0.01
Fasting insulin (IU/mL)	22.8±8.9	18.2±9.6	0.01
Triglyceride (mg/dL)	129.5±64.1	110.7±56.3	0.10
Cholesterol (mg/dL)	167.5±26.6	158.9±31.6	0.16
HDL (mg/dL)	44.6±8.17	44.8±9.7	0.92
LDL (mg/dL)	97.0±23.2	92±26.9	0.34
ALT (IU/L)	28.4±23.0	21.8±14.9	0.04
AST (IU/L)	24.5±11.3	21.3±7.3	0.05
TSH (IU/mL)	6.14±1.25	2.63±0.89	0.000
FT4 (ng/dL)	1.26±0.13	1.28±0.18	0.63
HOMA-IR	4.84±1.87	3.75±2.06	0.006
AI	0.42±0.26	0.35±0.25	0.18

Data are given as mean ±sd, SH, subclinical hypothyroid *BMI, Body Mass İndex; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; HDL, High-Density Lipoprotein; LDL Low-Density Lipoprotein; ALT,* Alanine aminotransferase; AST, Aspartate aminotransferase*; HOMAIR, Homeostasis Model Of İnsulin Resistance; AI, Atherogenic Index*

After the study group stratified into quartiles, we compared anthropometric and metabolic parameters in the first quartiles (TSH<25. Percentile) and fourth quartiles; fasting glucose, fasting insülin, HDL, ALT, AST, HOMA-IR, and AI were different (Table 2).

When the correlation between TSH and anthropometric and metabolic parameters were evaluated, there was a positive correlation between fasting glucose, insülin, triglyceride, ALT, AST, HOMA-IR and AI (Figure 1). Even after an adjustment for BMI, the variables still remained significantly associated with the mean TSH level except for triglyceride and AI. However, there was no correlation between TSH and age weight-SDS, height SDS, BMI-SDS, systolic and diastolic BP, total cholesterol HDL and LDL (p>0.05). A multiple regression analysis was carried out with TSH as dependent variables, and BMI-SDS, total cholesterol HDL, LDL and triglyceride as independent variables. It was demonstrated that TSH levels were significantly related to HOMA-IR value (p=0.001) (Table 3).

Table 2: Comparison of anthropometric and metabolic parameters according to first (TSH<2.08) and fourth (TSH>3.65) quartiles

	TSH<25p (n=56)	**TSH>75p** (n=56)	**p**
TSH (IU/mL)	2.63±0.89	6.14±1.25	0.000
BMI Z-score	2.39±0.81	2.34±0.63	0.74
Fasting glucose (mg/dL)	81.65±7.65	85.39±6.31	0.006
Fasting insulin (IU/mL)	17.54±9.43	22.1±1.1	0.01
Triglyceride (mg/dL)	106±53.66	122.24±55.88	0.125
Cholesterol (mg/dL)	167.5±26.6	158.9±31.6	0.16
HDL (mg/dL)	47.12±10.28	43.03±7.39	0.019
LDL (mg/dL)	93.35±25.27	89.53±25.52	0.43
ALT (IU/L)	18.78±8.44	27.7±21.3	0.005
AST (IU/L)	19.6±6.84	24.1±10.93	0.003
HOMA-IR	3.56±2.04	4.69±2.8	0.006
AI	0.30±0.27	0.41±0.23	0.025

Data are given as mean ±sd, TSH, thyroid stimulating hormone; *BMI, Body Mass İndex; HDL, High-Density Lipoprotein; LDL Low-Density Lipoprotein; ALT,* Alanine aminotransferase; AST, Aspartate aminotransferase*; HOMAIR, Homeostasis Model Of İnsulin Resistance; AI,*

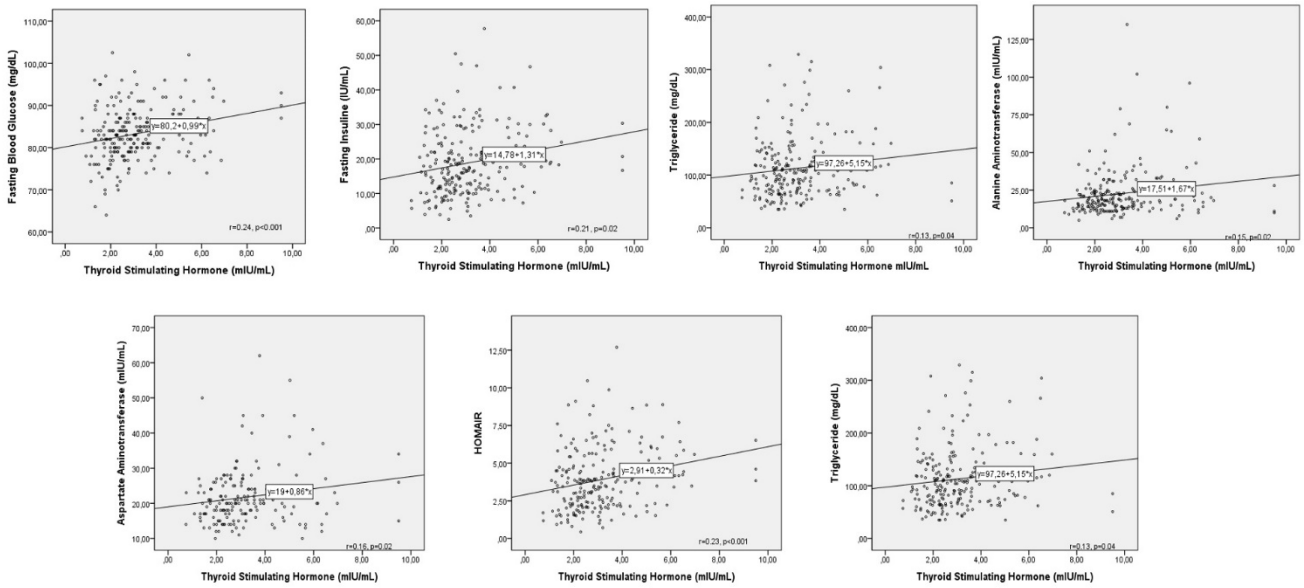

Figure 1: Correlations between TSH and several anthropometric and metabolic parameters

Table 3: Multiple regression analysis between TSH level with anthropometric and metabolic parameters

Variable	ß-Coefficient (95% CI)	p
BMI-SDS	-0.76 (-0.46-0.13)	0.28
TRİGLİCERİDE	-0.23 (-0.03-0.02)	0.64
CHOLESTEROL	0.81 (-0.09-0.17)	0.55
HDL	-0.24 (-0.17-0.09)	0.56
LDL	-0.69 (-0.17-0.09)	0.55
HOMA-IR	0.25 (0.08-0.29)	0.001

DISCUSSION

We found that TSH level was independently associated with HOMA-IR levels as a surrogate marker of insülin resistance in obese children and adolescents. Additionally, obese subjects with SH had higher serum transaminase levels when compared without SH. This data suggested that obese patients with SH may be more susceptible to metabolic complications than euthyroid subjects.

It has been shown that not only overt hypothyroidism but also SH is closely associated with insulin resistance that is one of the most important factors playing roles in the origin of the cardiovascular alterations and type 2 diabetes[14]. The genes that regulate glucose homeostasis at the liver and peripheral tissues are directly influenced by thyroid hormones[15]. We found that TSH level was independently associated with HOMA-IR levels. In a retrospective study that the patients were subdivided into two groups according to TSH level based on 2.5 µIU/mL, Individuals with TSH Levels >2.5 had higher HOMA-IR and lower HDL levels[16]. Similarly, Nader at al[17]. suggested that increased TSH level is associated with higher triglyceride levels and elevated HOMA-IR values. On the contrary, Cerbone at al[18]. showed that HOMA-IR value was not different in subjects with SH versus controls.

The relationship with hepatic steatosis and subclinical hypothyroidism has been recently shown in children[19;20]. In a retrospective study of 332 overweight or obese children and adolescents, Kaltenbach et al.[19] showed that higher TSH levels are associated with a greater degree of fatty infiltration on ultrasound imaging. Hypertransaminasemia, if other reasons exclude, is one of the important markers for hepatic steatosis in obese children and adolescents. In our study, slightly but significantly elevated hypretransaminasemia may be related to subtle hepatic steatosis. We also found that ALT and AST levels in obese subjects with SH were positively correlated with TSH levels. It has also been shown that SH associated with hepatic steatosis independently of metabolic risk factors. It is uncertain, how hypertrotropinemia exactly affects serum transaminase levels. It may be explained that thyroid hormones and hepatic steatosis share common genetic and environmental influences[21].

A positive association of TSH and anthropometric parameters in obese children and adolescents were reported in the literature[1;2;8;9;19;22;23]. Dahl et al.[22] showed that TSH concentrations were associated positively with waist-height ratio. However, we did not show a correlation with the severity of obesity (BMI-SDS) and TSH levels. Similarly, Kumar et al. failed to show any correlation between TSH and BMI-SDS. This discrepancy may be explained by small sample size. On the other hand, we use the BMI-SDS as a marker for the severity of obesity. However, there are limitations in use of BMI as a measure of adiposity for the pediatric population, due to variation in BMI with age, sex, puberty, and race or ethnicity [24;25]. Moreover, it was reported that BMI had a low sensitivity to determine the degree of adiposity [26].

The prevalence of SH is 4-20% in adults, and 1.5-3% in children[2]. On the other hand, obese children and adolescent have higher prevalence of SH than lean peers. In line with literature, the present study showed that prevalence of SH in obese children and adolescent is 14.1%. Elevated TSH levels seem to be a consequence instead of cause. Zhang et al.[23] showed that TSH level was positively correlated with waist circumference.

Moreover, several studies demonstrated that the TSH level tends to decrease with weight loss[27;28].

Our study has several limitations. First, the small sample size of the cohort might have failed to satisfy to conclude the subclinical hypothyroidism and ıts effects on metabolic parameters. Second, our study design was retrospective and cross-sectional, which may not provide definitive information about cause-and-effect relationships.

In conclusion, obese children and adolescents with SH have increased subclinical alterations of cardiovascular risk factors and higher risk for hepatic steatosis when compared without SH. Larger comprehensive prospective studies with an increased number of cases in each group are needed to explore the relationship between SH and metabolic alterations in obese children and adolescents with SH.

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