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Is Waist-height Ratio Associated with Thyroid Antibody Levels in Children with Obesity?

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What is already known on this topic?

It is known that obesity influences thyroid functions. Recently, it was reported that thyrotropin levels were associated with body mass index standard deviation score and waist-height ratio (WHtR)-an indicator of central fat accumulation-in obese children. In adults with obesity thyroid autoantibody levels were higher than healthy subjects. However, in children with obesity, thyroid autoimmunity is not considered as prevalent as in adults, as autoimmune thyroiditis was reported in only 19.5% of obese children with hyperthyrotropinemia. Although a correlation between WHtR and thyrotropin-thyroxine levels was found in obese children, its association with thyroid autoantibody levels still remains unclear.

What this study adds?

In our study, children with obesity had higher concentrations of thyroid autoantibodies compared to healthy controls, although these levels remained below the cut-off for clinical significance. The obese patients with a WHtR >0.6 had higher thyroid antibody levels compared to those with a WHtR ≤0.6, even in the absence of autoimmune thyroid disease, and there was a positive correlation between WHtR and thyroglobulin-antibodies levels. These findings suggest that central adiposity influences thyroid autoantibody production in children with obesity.

Abstract

Objective: Obesity is known to affect thyroid function. Recently, waist-height ratio (WHtR) has been considered as a useful marker of subclinical hypothyroidism in obese cases, but its relation with thyroid autoimmunity still remains unclear. We evaluated the effect of body fat mass, WHtR, and metabolic parameters on thyroid autoantibody levels in children with obesity.

Methods: This was a cross-sectional study carried out with an obese [n=56, male/female (M/F): 29/26] and a healthy group (n=38, M/F: 19/19). All subjects underwent anthropometric measurements, laboratory investigations for thyroid function tests, thyroid peroxidase (TPO-ab) and thyroglobulin-antibodies (Tg-ab), transaminases, blood glucose, insulin levels, and lipids after overnight fasting; homeostatic model assessment for insulin resistance (HOMA-IR) was calculated for assessment of insulin resistance. Fat mass was estimated by multiple frequency bioimpedance analysis in the obese group, which was further divided into two subgroups according to the median of WHtR. All parameters were compared between the groups/subgroups.

Results: In the obese group, weight, height, body mass index (BMI), free triiodothyronine, thyrotropin, TPO-ab, insulin, low density lipoprotein-cholesterol, total cholesterol, alanine aminotransferase levels, and HOMA-IR were significantly higher than the controls group ($p<0.05$ for all). Median of WHtR was 0.6 in the obese group. In the "WHtR >0.6" subgroup (n=28), weight, BMI, fat mass, TPO-ab, Tg-ab, insulin and triglyceride levels were higher than WHtR ≤0.6 subgroup ($p<0.05$). A positive correlation was obtained between Tg-ab and WHtR (rho=0.28, $p=0.041$).

Conclusion: Euthyroid children with obesity and a WHtR >0.6 are likely to have higher thyroid antibody levels, and Tg-ab levels have a positive correlation with WHtR, which reveals an association of central adiposity with thyroid autoantibody levels in these cases.

Keywords: Free thyroxine, free triiodothyronine, thyroglobulin antibody, thyroid peroxidase antibody, thyroid stimulating hormone, waist-height ratio

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Introduction

Obesity leads to a number of metabolic and hormonal disturbances in children, such as thyroid dysfunction (1,2). Moderate elevation of thyrotropin (TSH) levels (subclinical hypothyroidism) is a common condition in children with overweight/obesity, with a prevalence ranging from 7% to 23%. However, prior studies offer conflicting results about thyroid hormone levels (2-12). Nonetheless, it is accepted that TSH and thyroid hormone levels usually normalize with weight loss, from which it was interpreted that this is an adaptive response to lipid accumulation (2,3,4).

Anthropometric measurements are mostly used to diagnose and evaluate obesity and its complications (1). To date, numerous studies have reported a positive correlation between body mass index (BMI) and TSH, and some follow-up studies have demonstrated that TSH level increased with weight gain and decreased with weight loss (2,3,4,5,6,7,8,9). Besides, some other anthropometric measurements have also been evaluated in several studies (1,4,5,6,8,9). In a study with a large cohort, TSH levels were reported to be associated positively with BMI standard deviation (SD) score (SDS) and waist/height ratio (WHtR), regardless of age, gender and pubertal stage. However, serum free thyroxine (fT4) concentrations were found to be associated only with WHtR (5). In another study, waist/hip ratio was considered as a predictor of increased free triiodothyronine (fT3) to fT4 ratio (9). These results suggest that central obesity could increase the risk of concurrent thyroid abnormalities in children with obesity (5,9).

Although TSH and thyroid hormone levels in children and adults with obesity have been evaluated in numerous studies, the effect of obesity and lipid accumulation on thyroid autoantibody levels still remains unclear in children (2,3,4,5,6,7,8,9,10,11,12). Obesity is well known to be a chronic inflammatory process (1). Elevated thyroid autoantibody levels, especially antithyroid peroxidase (TPO-ab), with hypothyroidism have been reported to be common in adults with obesity (10). In addition, increased leptin levels have been found to be associated with the presence of autoimmune thyroiditis disease (AITD) (10). However, results of studies of childhood obesity are slightly different, and non-autoimmune thyroiditis should be considered in the differential diagnosis before diagnosing AITD (3,12,13). It was reported that obese cases with hyperthyrotropinemia and hypoechogenicity on thyroid ultrasound, but without thyroid autoantibody seropositivity, had normal cytological findings in ultrasound-guided fine needle aspiration biopsy specimens, which indicates the important role of thyroid antibodies in a diagnosis of AITD in obese patients (13). AITD was detected in only 19.5% of children with obesity and hyperthyrotropinemia and in 7.4% of children with normal TSH levels (3,12). Moreover, it has been shown that TPO-ab level was positively associated with BMI (7).

Obesity and central fat accumulation lead to insulin resistance and dyslipidemia (1). In previous studies, TSH levels were found to correlate with fasting insulin (6), total cholesterol (6,11), triglyceride levels (6,8,11,14) and homeostatic model assessment for insulin resistance (HOMA-IR) (6). However, little is known about the association of thyroid antibody levels and metabolic disturbances in children with obesity.

The aim of this study was to evaluate the association of thyroid hormone and thyroid autoantibody levels with body fat mass, WHtR and metabolic parameters, such as lipid profile, fasting glucose and insulin levels in euthyroid children with obesity.

Methods

Study Population

In this cross-sectional study, 55 obese and 38 healthy children aged between 8 and 18 years were involved. The obese group consisted of subjects without additional endocrine/genetic disorders leading to obesity. The control group consisted of age-and sex-matched children who were admitted to the pediatric clinic for routine health screening. Cases who were previously diagnosed with overt or subclinical hypothyroidism, AITD, who had a family member with a diagnosis of AITD or who were receiving medication affecting energy metabolism, such as metformin, were excluded from the study.

Anthropometric Measurements and Puberty Staging

All anthropometric measurements were obtained by the same clinician on subject admission. Height was measured using a stadiometer (Holtain Limited, Crymych, Wales) to the nearest 0.5 cm with the subject having bare feet, eyes looking straight ahead and back against the wall. Weight was measured using an electronic scale (Tefal, France) sensitive to 100 g and BMI was calculated as weight in kilograms divided by the square of height in meters. The waist circumference (WC) was measured in the obese group as an abdominal circumference in the horizontal plane midway between the lowest rib and the superior border of iliac crest and at the end of normal expiration with a non-stretchable tape to the nearest 0.1 cm. The SDS and percentiles were calculated according to Turkish pediatric reference values previously reported by ÇEDD Çözüm/TPEDS Metrics (15,16). The patients with BMI percentile ≥95 for sex and age were

defined as obese (1). Puberty stage was reported using the method of Marshall and Tanner (17).

Assessment of Body Composition

Body composition including fat mass (kg) was estimated by multiple frequency bioimpedance analysis in the obese group. Measurements were performed by a single physician using a portable body bioimpedance spectroscopy device, the Body Composition Monitor (Fresenius Medical Care, Germany). Fat mass index (FMI) was calculated as the quotient of fat mass/height^2. Fat mass to weight ratio (fat%) was described as the quotient of fat mass/body weight x 100. All anthropometric measurements and body composition analyses were carried out at the same study visit and obtained after overnight fasting.

Blood Sample Collection

Serum specimens collected from the patient and control groups were stored at -80 °C until analysis. Routine biochemical tests were analyzed in the Central Biochemistry Laboratory, Cerrahpaşa Faculty of Medicine, İstanbul. Fasting blood glucose, total cholesterol, high density lipoprotein-cholesterol (HDL-C), low density lipoprotein-cholesterol and triglyceride concentrations were measured by enzymatic colorimetric methods, while aspartate aminotransferase and alanine aminotransferase (ALT) were assayed by kinetic ultraviolet methods on a Roche Modular System (Cobas, Roche GmbH, Germany). Insulin concentration was measured by solid phase sandwich enzyme-linked immunosorbent assay (DRG instruments GmbH, Germany). Insulin resistance was assessed using HOMA-IR, which was calculated using the following standard formula: glucose (mg/dL) x insulin (μIU/mL)/405 (18).

Thyroid Function and Autoantibody Tests

For quantitative analysis of fT3 [DRG Instruments GmbH, Germany, Catalog No: enzyme immunoassay (EIA)-2385; intra-assay CV 3.6%, inter-assay CV 7.9%], fT4 (DRG Instruments GmbH, Germany, Catalog No: EIA-2386; intra-assay CV 4.26%; inter-assay CV 6.01%), and TSH (DRG Instruments GmbH, Germany, Catalog No: EIA-4171; intra-assay CV 5.7%; inter-assay CV 7.1%) commercial EIA kits were used, according to the manufacturer's guidelines.

A TSH level <5 μU/mL was defined as "normal"; and, reference intervals for fT4 and fT3 levels were 0.7-1.6 ng/dL and 1.71-3.72 pg/mL respectively (19). The patients were considered to be euthyroid if their serum fT4 and TSH levels were within normal range (19). TPO-ab and thyroglobulin-antibodies (Tg-ab) levels were measured by chemiluminescence method using the Roche Modular System (Cobas, Roche GmbH, Germany). Intra-assay CV and inter-assay CV for TPO-ab were 4.1 and 6.1 respectively. For Tg-ab, intra-assay CV and inter-assay CV were 2.1 and 4.6. A TPO-ab level >34 IU/mL and a Tg-ab level >115 IU/mL were described as "positive".

The study was approved by the İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine Ethical Committee (date: 04.02.2020 and ethics approval number: 21299). Patients were included in the study following a consent form signed by parents/caregivers. The information about the patients was kept confidential and used only for the purposes of the study.

Statistical Analysis

All data were assessed for normal distribution using Shapiro-Wilk test. Normally distributed data were presented as mean ± SD, and nonparametric data were presented as median (interquartile range). Between group comparisons were made using Fisher's exact test or Mann-Whitney U test, according to a normal or a nonparametric distribution of the tested variable. Pearson's correlation was used to investigate the relation between normally distributed quantitative data, while Spearman's rank correlation was used otherwise. Obese cases were divided into two different groups according to the median value of WHtR. The association between thyroid antibodies and WHtR were tested with univariate analysis in the obese group. Biostatistical analysis of the study results was performed by Statistical Package for Social Sciences software, version 21.0 (SPSS Inc., Chicago, IL, USA) and p values <0.05 were considered statistically significant.

Results

The study subjects consisted of obese [n = 55, male/female (M/F): 29/26] and healthy groups (n = 38, M/F: 19/19) with a mean age of 12.4 ± 2.6 years. A majority (78.5%, n = 73) of the patients were pubertal. Between the two groups, age, gender and pubertal stages were similar ($p>0.05$). Serum TSH, fT4, fT3 and thyroid autoantibody levels of all subjects were within normal ranges. Weight and weight SDS, BMI and BMI SDS were higher in the obese group compared to controls, as expected. In laboratory findings, fasting insulin, ALT, fT3, TSH, TPO-ab levels and HOMA-IR were higher, and fT4 was lower in children with obesity than the controls ($p<0.001$). Anthropometric measurements, metabolic parameters, thyroid function test and autoantibody levels are summarized in Table 1.

The mean value of the WC, WHtR, fat% and FMI of obese patients were 97.3 ± 13.6, 0.61 ± 0.06, 39.2 ± 5.7 and 16.6 ± 4.2, respectively.

Table 1. Comparison of anthropometric measurements, metabolic parameters, thyroid function test and autoantibody levels between the obese and control group

		Obese group (n = 55)	Control group (n = 38)	
Variable		**Mean ± SDS Median (IQR) (minimum-maximum)**	**Mean ± SDS Median (IQR) (minimum-maximum)**	**p**
Age, year		12.6 ± 2.6 (7.1-17.3)	12 ± 2.7 (7.3-17.5)	0.25*
Gender	Female	26 (47.3)	19 (50)	0.796**
n (%)	Male	29 (52.7)	19 (50)	
Puberty	Prepubertal	11 (20)	9 (23.7)	0.67**
n (%)	Pubertal	44 (80)	29 (76.3)	
Weight (kg)		76 (29.5) (31.2-122.9)	42.7 (24.1) (23-65)	**< 0.001***
Weight SDS		2.82 (1.17) (0.94-4.46)	-0.12 (1.44) (-1.23-1.18)	**< 0.001***
Height (cm)		158.7 ± 13.7 (125-188)	149.8 ± 15 (123.8-175)	**0.004***
Height SDS		0.86 ± 1.1 (-1.52-4.12)	0.01 ± 0.9 (-1.74-1.72)	**< 0.001***
BMI		29.9 (7.2) (20-37.2)	18.7 (5.2) (14.3-23.9)	**< 0.001***
BMI SDS		2.59 (0.81) (1.65-3.65)	-0.11 (1.44) (-1.83-1.14)	**< 0.001***
BMI percentile		99.5 (1.5) (95.1-99.9)	44 (52) (3.5-84)	**< 0.001***
fT3, pg/dL		4.02 (0.96) (1.0-6.23)	3.13 (0.96) (1.19-4.96)	**< 0.001***
fT4, ng/dL		1.02 ± 0.14 (0.71-1.39)	1.15 ± 0.16 (0.81-1.52)	**< 0.001***
TSH, IU/L		2.01 (1.06) (0.74-4.62)	1.46 (0.74) (0.51-4.18)	**< 0.001***
TPO-ab, IU/mL		13 (10) (5-29)	7 (6) (5-20)	**< 0.001***
Tg-ab, IU/mL		17 (12) (10-60)	15 (7) (8-26)	0.19***
Fasting glucose, mg/dL		90 (9) (66-100)	92 (6) (71-100)	0.81***
Fasting insulin, uU/mL		19 (13.5) (2.4-88.3)	8.1 (5.8) (1-20.6)	**< 0.001***
HOMA-IR		4.6 (3.4) (0.56-17.9)	1.9 (1.3) (0.7-3.22)	**< 0.001***
Triglyceride, mg/dL (n = 88)		86 (50) (21-188)	78 (46) (18-169)	0.09***
HDL-C, mg/dL (n = 88)		50 (14) (29-83)	60 (25) (4-84)	0.113***
LDL-C, mg/dL (n = 88)		93 (31) (48-187)	82 (35) (41-110)	**0.036***
Cholesterol, mg/dL (n = 88)		162 (40) (119-255)	150 (35) (106-178)	**0.041***
AST, IU/L (n = 91)		20 (6) (11-45)	22 (6) (12-31)	0.429***
ALT, IU/L (n = 91)		17 (12) (8-79)	15 (7) (7-25)	**0.001***

*: T-test, **: Chi-square test, ***: Mann-Whitney U test.
ALT: alanine aminotransferase, AST: aspartate aminotransferase, BMI: body mass index, SDS: standard deviation score, fT4: free thyroxine, fT3: free triiodothyronine, HDL-C: high-density lipoprotein cholesterol, HOMA-IR: homeostasis model assessment of insulin resistance, LDL-C: low-density lipoprotein cholesterol, Tg-ab: thyroglobulin antibody, TPO-ab: thyroid peroxidase antibody, TSH: thyroid stimulating hormone

In, children with obesity , WHtR was significantly correlated with Tg-ab ($p = 0.041$, $r = 0.28$), triglyceride level ($p = 0.011$, $r = 0.35$), fat% ($p < 0.001$, $r = 0.52$) and FMI ($p < 0.001$, $r = 0.62$) (Figure 1).

Although the cut-off value of WHtR for predicting subclinical hypothyroidism has previously been proposed as 0.5 (5), in our cohort, there was no significant difference in thyroid antibody levels between the patients with a WHtR above and below 0.5 ($p > 0.05$). As no other cut-off value has been reported to predict an increase in thyroid antibody levels, the obese cases were divided into two different groups according to the median WHtR, which was 0.6: patients with a WHtR ≤0.6 and patients with a WHtR >0.6. As expected, in the WHtR >0.6 group, weight, weight SDS, BMI and BMI SDS were significantly higher, as well as fat% and FMI than the WHtR ≤0.6 group. Although no significant difference was obtained for TSH and thyroid hormone levels, both thyroid autoantibody levels were significantly higher in the WHtR >0.6 group. Among the metabolic parameters, triglyceride and fasting insulin levels were significantly higher in the WHtR >0.6 group ($p < 0.05$) (Table 2). Anthropometric measurements, metabolic parameters, thyroid function

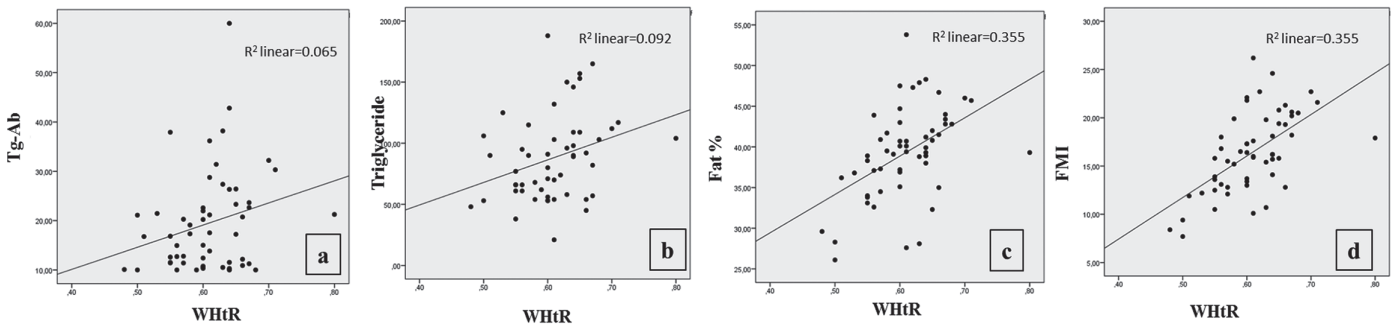

Figure 1. a. b. c. d. Waist/height ratio associated with thyroid antibody levels in obese children

WHtR: waist/height ratio, Tg-ab: thyroglobulin antibody, FMI: fat mass index

test and autoantibody levels of the two subgroups are summarized in Table 2.

Univariate analysis revealed a significant difference in TPO-ab and Tg-ab levels between WHtR ≤0.6 and WHtR >0.6 subgroups with an odds ratio (OR) of 0.262 and 0.275 respectively (Table 2).

Discussion

This study identified an association between WHtR and thyroid antibody levels, particularly Tg-ab. Thyroid antibody levels were higher in patients with obesity, concurrent with elevated WHtR, BMI and BMI SDS, fat mass, fasting insulin and triglyceride levels, which may suggest that lipid accumulation and particularly central obesity may influence thyroid autoantibody production.

In this study, fT3 and TSH levels were significantly higher and fT4 levels were significantly lower in euthyroid children with obesity compared to controls. Although there are some studies with diverse outcomes, our results are similar to those of Marwaha et al (7), who showed higher TSH and fT3 levels and lower fT4 levels in obese euthyroid children. Leptin effect, enhanced deiodination of thyroid hormones, blunted feed-back response of TSH release to circulating fT3, promoting action of TSH on adiposity and insulin resistance have all been considered as the probable causes of this condition (7).

Anthropometric measurements, such as BMI SDS and WHtR have been recently associated with TSH and thyroid hormones (4,5,6,8). Dahl et al (5) reported that TSH concentrations were associated positively with WHtR, and they concluded that the OR of exhibiting subclinical hypothyroidism was 1.8 when presenting with a WHtR >0.5. However, no cut off value of WHtR was reported to predict an increase in thyroid autoantibody levels. Our study revealed that children with obesity and a WHtR >0.6 (the median value of the obese group) had significantly higher TPO-ab and Tg-ab levels even in the absence of hyperthyrotropinemia with an OR of 0.262 and 0.275 respectively, and in these patients BMI, BMI SDS, fat% and FMI were significantly higher. Anthropometric and biometric measurements such as BMI, BMI SDS, fat%, FMI and WHtR have been associated with lipid accumulation, and changes in the concentrations of adipocytokines, such as leptin and some other inflammatory markers (1). It has previously been shown that leptin played a role in the regulation of the T helper-1 response and the proliferation of CD4+ and CD25+ cell clone involved in the apoptotic process leading to AITD (20,21). In adults, leptin concentration has also been associated with AITD regardless of bioanthropometric variables (10). In this study, a weak but significant, positive correlation between WHtR and Tg-ab level was identified, but no significant correlation was obtained between BMI and Tg-ab levels in obese children with obesity. Thus, we suggest that abdominal obesity may be a better predictor of thyroid autoimmunity than BMI in obese cases, which only reflects the obesity degree rather than its distribution.

Our results indicate that the concentrations of thyroid antibodies appeared to increase, despite the absence of thyroid dysfunction, hyperthyrotropinemia and autoantibody levels below the cut-off values. in children with obesity. Also, in children with obesity and a WHtR >0.6, thyroid antibody levels, and in particular Tg-ab, were higher and only Tg-ab levels were found to be correlated with central fat accumulation; no such association was found for TPO-ab levels.

The TPO-ab and Tg-ab positivities have been reported to be 12-26% and 10.5% in healthy adults; and 15% and 14% in adults with obesity (22,23,24). The increase in thyroid autoantibodies may result from both AITD and obesity, "Does this finding complicate the diagnosis and management of AITD in children with obesity?", in other words, "Does the increase in antibody levels suggest AITD or is it just the result of obesity?". We suggest that it is unnecessary to

Table 2. Comparison of anthropometric measurements, metabolic parameters, thyroid function test and autoantibody levels between the WHtR ≤0.6 and WHtR > 0.6 subgroups

		WHtR ≤0.6 (n = 27) (minimum-maximum)	WHtR > 0.6 (n = 28) (minimum-maximum)		OR (95% CI)
Variable		**Mean ± SDS Median (IQR)**	**Mean ± SDS Median (IQR)**	**p**	
Age, year		12 ± 2.7 (7.1-15.8)	13.3 ± 2.4 (9.3-17.3)	0.054*	
Gender	Female	12 (22)	14 (25.5)	0.68**	
n (%)	Male	15 (27)	14 (25.5)		
Puberty	Prepubertal	6 (11)	5 (9)	0.686**	
n (%)	Pubertal	21 (38)	23 (42)		
Weight (kg)		69.4 (31.1) (31.2-111.3)	85.5 (30.5) (56-122.9)	**0.011*** **	
Weight SDS		2.37 (1.7) (0.94-4.34)	2.95 (0.8) (1.5-4.46)	0.083***	
Height (cm)		156.1 ± 15.3 (125-186)	161.1 ± 11.8 (142.2-188)	0.183*	
Height SDS		1.08 ± 1.28 (-1.52-4.12)	0.65 ± 0.9 (-1.35-2.15)	0.152*	
BMI		27.3 (4.6) (20-35.8)	32.9 (5.6) (26.7-37.2)	**< 0.001*** **	
BMI SDS		+ 2.2 (0.78) (1.65-3.48)	+ 2.83 (0.5) (1.98-3.65)	**0.001*** **	
BMI (%)		99.6 (1.5) (95.1-99.9)	99.8 (0.6) (97.6-99.9)	**0.001*** **	
fT3, pg/dL		4.02 (1.04) (1.0-6.23)	4.05 (0.86) (1.0-5.74)	0.395***	
fT4, ng/dL		1.01 ± 0.15 (0.77-1.34)	1.04 ± 0.13 (0.71-1.39)	0.55*	
TSH, IU/L		1.96 (0.88) (1.24-4.01)	2.03 (1.46) (0.74-4.62)	0.655***	
TPO-ab, IU/mL		11 (8) (5-29)	16 (10) (6-25)	**0.023*** **	**0.262**
Tg-ab, IU/mL		13 (10) (10-38)	22 (18) (10-60)	**0.009*** **	**0.275**
Fasting glucose, mg/dL		92 (10) (80-100)	89 (10) 66-100)	0.269***	
Fasting insulin, uU/mL		17.7 (10) (2.4-39.8)	26.7 (14.3) (6.5-88.3)	**0.029*** **	
HOMA-IR		3.9 (2) (0.56-8)	5.7 (3.9) (1.5-17.9)	0.076***	
Triglyceride, mg/dL (group 1 n = 26) (group 2 n = 26)		66 (36) (38-188)	98 (47) (21-165)	**0.019*** **	
HDL-C, mg/dL (group 1 n = 26) (group 2 n = 26)		51 (17) (35-83)	49 (13) (29-71)	0.213***	
LDL-C, mg/dL (group 1 n = 26) (group 2 n = 26)		95 (30) (48-187)	92 (34) (67-146)	0.833***	
Cholesterol, mg/dL (group 1 n = 26) (group 2 n = 26)		164 (43) (119-255)	159 (35) (128-213)	0.184***	
AST, IU/L (group 1 n = 26) (group 2 n = 28)		19 (6) (12-45)	21 (7) (11-40)	0.728***	
ALT, IU/L (group 1 n = 26) (group 2 n = 28)		15 (9) (9-79)	22 (14) (8-42)	0.112***	
Fat%		37.3 ± 5 (26.1-47.5)	41.1 ± 5.5 (27.6-53.8)	**< 0.001***	
FMI		14.5 ± 3.6 (7.7-22.1)	18.2 ± 3.9 (10.1-26.2)	**< 0.001***	

*: T-test, **: Chi-square test, ***: Mann-Whitney U test.
ALT: alanine aminotransferase, AST: aspartate aminotransferase, BMI: body mass index, SDS: standard deviation score, Fat%: Fat mass/weight ratio, FMI: Fat mass index, fT4: free thyroxine, fT3: free triiodothyronine, HDL-C: high-density lipoprotein cholesterol, HOMA-IR: homeostasis model assessment of insulin resistance, LDL-C: low-density lipoprotein cholesterol, Tg-ab: thyroglobulin antibody, TPO-ab: thyroid peroxidase antibody, TSH: thyroid stimulating hormone, WHtR: waist/height ratio, CI: confidence interval

routinely investigate thyroid antibody levels in children with obesity, especially when thyroid function tests are within normal limits. In cases of seropositivity, a certain distinction of AITD may be challenging, given that thyroid changes in ultrasound is a common finding in cases with obesity (12). Further long-term follow-up studies investigating if weight loss reverses the abnormal findings in ultrasound and leads to a decrease in levels of thyroid autoantibodies would shed light on this topic.

As expected, fasting insulin and triglyceride levels were significantly higher in the WHtR >0.6 subgroup compared to the WHtR ≤0.6 subgroup, as high WHtR is associated with high fat mass and central lipid accumulation (1,9). The relation between thyroid function tests and lipid profile in obese subjects shows variations in different studies. Unüvar et al (8) previously reported that triglyceride level was the strongest independent variable correlated with TSH level in children with obesity. Shalitin et al (14) found a positive correlation between TSH and triglyceride levels, whereas Reinehr at al (25) could not find any correlation between TSH and lipid profile in their study conducted with 246 children with obesity.

Despite a large number of studies on thyroid hormones and TSH in childhood obesity, there are few data concerning the association between thyroid autoantibody levels and metabolic parameters of obesity, such as insulin/glucose levels, HOMA-IR, and lipid profile. We did not find any correlation between these parameters and thyroid antibody levels. It has recently been shown that TPO-ab and Tg-ab levels were not significantly different in obese children with and without insulin resistance (9). In adults with obesity, no association was found between thyroid antibody positivity, insulin resistance and atherogenic dyslipidemia (23). However, Tamer et al (26) reported that TPO-ab levels positively correlated with triglyceride levels and WC, and negatively correlated with HDL-C levels in premenopausal women with Hashimoto thyroiditis, whereas Tg-ab level correlated with triglyceride and non-HDL-C levels. In these patients, no correlation was found between TSH levels and lipid profile. The investigators suggested that thyroid autoimmunity could be associated with hyperlipidemia, independent of thyroid function. The association between thyroid antibody levels and insulin resistance and/or lipid profile still remains unclear and further investigations in adults and children are needed.

Study Limitations and Strength

Ultrasound imaging of thyroid glands was not performed. However, this is a minor setback because thyroid changes on ultrasound may also be due to non-autoimmune thyroiditis, which has been associated with obesity in a pediatric population (12). Due to limited sample sizes and study design, we could not obtain a cut-off value of WHtR to predict the presence of thyroid autoimmunity. Nevertheless, univariate analysis showed a significant difference in TPO-ab and Tg-ab levels when we divided the obese subjects into two subgroups, according to the median WHtR value "0.6" in our cohort of children with obesity. Iodine levels were not studied which can also be effective in thyroid autoimmunity. Mediators such as leptin, adiponectin and resistin which may have a link between autoimmunity and fat accumulation were not studied.

The strength of the study is that the impact of lipid accumulation (estimated by bioelectrical impedance analysis) and central adiposity (described by WHtR) on thyroid function and autoantibodies were both evaluated, and their association with metabolic parameters was fully investigated.

Conclusion

This study showed that euthyroid children with obesity had higher concentrations of thyroid autoantibodies compared to controls, although these levels remained below the cut-off for clinical significance. In addition, the obese patients with a WHtR >0.6 had higher thyroid antibody levels compared to those with WHtR ≤0.6, even in the absence of AITD, and there was a positive correlation between WHtR and Tg-ab levels. These findings suggest that central adiposity influences thyroid autoantibody production in children with obesity. Further studies with larger number of participants are needed to determine the effect of central adiposity and its modulation of thyroid autoimmunity and the efficacy of the WHtR parameter in clinical practice concerning thyroid autoimmunity in obesity.

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Ethics

Ethics Committee Approval: The study was approved by the İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine Ethical Committee (date: 04.02.2020 and ethics approval number: 21299).

Informed Consent: Patients were included in the study following a consent form signed by parents/caregivers. The information about the patients was kept confidential and used only for the purposes of the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Bahar Özcabı, Gürkan Tarçın, Esma Şengenç, Feride Tahmiscioğlu Bucak, Concept: Olcay Evliyaoğlu, Bahar Özcabı, Design: Olcay Evliyaoğlu, Bahar Özcabı, Data Collection or Processing: Bahar Özcabı, Gürkan Tarçın, Esma Şengenç, Feride Tahmiscioğlu Bucak, Analysis or Interpretation: Bahar Özcabı, Olcay Evliyaoğlu, Literature Search: Bahar Özcabı, Gürkan Tarçın, Esma Şengenç, Feride Tahmiscioğlu Bucak, Olcay Evliyaoğlu, Writing: Bahar Özcabı, Gürkan Tarçın, Esma Şengenç, Feride Tahmiscioğlu Bucak, Oya Ercan, İbrahim Murat Bolayırlı, Olcay Evliyaoğlu.

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References

1. Kumar S, Kelly AS. Review of Childhood Obesity: From Epidemiology, Etiology, and Comorbidities to Clinical Assessment and Treatment. Mayo Clin Proc 2017;92:251-265. Epub 2017 Jan 5
2. Reinehr T. Obesity and thyroid function. Mol Cell Endocrinol 2010;316:165-171. Epub 2009 Jun 18
3. Eliakim A, Barzilai M, Wolach B, Nemet D. Should we treat elevated thyroid stimulating hormone levels in obese children and adolescents? Int J Pediatr Obes 2006;1:217-221.
4. Grandone A, Santoro N, Coppola F, Calabrò P, Perrone L, Del Giudice EM. Thyroid function derangement and childhood obesity: an Italian experience. BMC Endocr Disord 2010;10:8.
5. Dahl M, Ohrt JD, Fonvig CE, Kloppenborg JT, Pedersen O, Hansen T, Holm JC. Subclinical hypothyroidism in Danish lean and obese children and adolescents. J Clin Res Pediatr Endocrinol 2017;9:8-16. Epub 2016 Sep 9
6. Lundbäck V, Ekbom K, Hagman E, Dahlman I, Marcus C. Thyroid-stimulating hormone, degree of obesity, and metabolic risk markers in a cohort of Swedish children with obesity. Horm Res Paediatr 2017;88:140-146. Epub 2017 Jun 14
7. Marwaha RK, Tandon N, Garg MK, Ganie MA, Narang A, Mehan N, Bhadra. Impact of body mass index on thyroid functions in Indian children. Clin Endocrinol (Oxf) 2013;79:424-428. Epub 2013 May 11
8. Unüvar T, Anık A, Catlı G, Esen I, Abacı A, Büyükgebiz A, Böber. Isolated hyperthyrotropinemia in childhood obesity and its relation with metabolic parameters. J Endocrinol Invest 2014;37:799-804. Epub 2014 Jun 12
9. Răcătăianu N, Leach NV, Bolboacă SD, et al. Interplay between metabolic and thyroid parameters in obese pubertal children. Does visceral adipose tissue make the first move? Acta Clin Belg. 2019;24:1-9.
10. Marzullo P, Minocci A, Tagliaferri MA, Guzzaloni G, Di Blasio A, De Medici C, Aimaretti G, Liuzzi A. Investigations of thyroid hormones and antibodies in obesity: leptin levels are associated with thyroid autoimmunity independent of bioanthropometric, hormonal and weight-related determinants. J Clin Endocrinol Metab 2010;95:3965-3972. Epub 2010 Jun 9
11. Aypak C, Türedi O, Yüce A, Görpelioğlu S. Thyroid-stimulating hormone (TSH) level in nutritionally obese children and metabolic co-morbidity. J Pediatr Endocrinol Metab 2013;26:703-708.
12. Dursun F, Atasoy Öztürk T, Seymen Karabulut G, Kırmızıbekmez H. Obesity-related thyroiditis in childhood: relationship with insulin resistance. J Pediatr Endocrinol Metab 2019;32:471-478.
13. Radetti G, Kleon W, Buzi F, Crivellaro C, Pappalardo L, di Iorgi N, Maghnie M. Thyroid function and structure are affected in childhood obesity. J Clinical Endocrinol Metab 2008;93:4749-4754. Epub 2008 Oct 7
14. Shalitin S, Yackobovitch-Gavan M, Phillip M. Prevalence of thyroid dysfunction in obese children and adolescents before and after weight reduction and its relation to other metabolic parameters. Horm Res 2009;71:155-161. Epub 2009 Feb 3
15. Demir K, Özen S, Konakçı E, Aydın M, Darendeliler F. A Comprehensive Online Calculator for Pediatric Endocrinologists: ÇEDD Çözüm/TPEDS Metrics. J Clin Res Pediatr Endocrinol 2017;9:182-184. Epub 2017 Apr 26
16. Neyzi O, Bundak R, Gökçay G, Günöz H, Furman A, Darendeliler F, Baş F. Reference values for weight, height, head circumference, and body mass index in Turkish children. J Clin Res Pediatr Endocrinol 2015;7:280-293.
17. Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. Arch Dis Child 1969;44:291-303.
18. Keskin M, Kurtoglu S, Kendirci M, Atabek ME, Yazici C. Homeostasis model assessment is more reliable than the fasting glucose/insulin ratio and quantitative insulin sensitivity check index for assessing insulin resistance among obese children and adolescents. Pediatrics 2005;115:500-503. Epub 2005 Mar 1
19. Takata K, Amino N, Kubota S, Sasaki I, Nishihara E, Kudo T, Ito M, Fukata S, Miyauchi A. Benefit of short-term iodide supplementation to antithyroid drug treatment of thyrotoxicosis due to Graves' disease. Clin Endocrinol (Oxf) 2010;72:845-850. Epub 2009 Nov 11
20. De Rosa V, Procaccini C, Calì G, Pirozzi G, Fontana S, Zappacosta S, La Cava A, Matarese G. A key role of leptin in the control of regulatory T cell proliferation. Immunity 2007;26:241-255.
21. Zhang W, Kudo H, Kawai K, Fujisaka S, Usui I, Sugiyama T, Tsukada K, Chen N, Takahara T. Tumor necrosis factor-alpha accelerates apoptosis of steatotic hepatocytes from a murine model of non-alcoholic fatty liver disease. Biochem Biophys Res Commun 2010;391:1731-1736. Epub 2009 Dec 31
22. Prummel MF, Wiersinga WM. Thyroid peroxidase autoantibodies in euthyroid subjects. Best Pract Res Clin Endocrinol Metab 2005;19:1-15.
23. Temizkan S, Balaforlou B, Ozderya A, Avci M, Aydin K, Karaman S, Sargin M. Effects of thyrotropin, thyroid hormones and thyroid antibodies on metabolic parameters in a euthyroid population with obesity. Clin Endocrinol (Oxf) 2016;85:616-623. Epub 2016 May 26
24. Yan YR, Gao XL, Zeng J, Liu Y, Lv QG, Jiang J, Huang H, Tong NW. The association between thyroid autoantibodies in serum and abnormal function and structure of the thyroid. J Int Med Res 2015;43:412-423. Epub 2015 Apr 8
25. Reinehr T, de Sousa G, Andler W. Hyperthyrotropinemia in obese children is reversible after weight loss and is not related to lipids. J Clin Endocrinol Metab 2006;91:3088-3091. Epub 2006 May 9
26. Tamer G, Mert M, Tamer I, Mesci B, Kilic D, Arik S. Effects of thyroid autoimmunity on abdominal obesity and hyperlipidaemia. Endokrynol Pol 2011;62:421-428.