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Relationships among thyroid hormones and obesity severity, metabolic syndrome and its components in Turkish children with obesity

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Abstract

Background: **we investigated the relationships between thyroid function and obesity severity, metabolic syndrome (MS) and MS components in 260 obese children and adolescents 10–17 years of age.**

Objectives: **we aimed to determine the association of thyroid functions with obesity severity and the components of metabolic syndrome (MS) in pediatric obese patients.**

Methods: **only obese children and adolescents were included, and divided the obese children into three groups according to body mass index (BMI)-SDS quartiles. The first quartile was group 1, the second and third quartiles were group 2, and the fourth quartile was group 3. Group 3 indicated severe obesity. The modified WHO criteria adapted for children were used to diagnose MS. We assessed anthropometric data and serum biochemical parameters, including the lipid profile and fasting glucose (FG), insulin, thyroid-stimulating hormone (TSH), free thyroxine (fT4), and free triiodothyronine (fT3) levels. Blood pressure (BP) was measured with a standard digital sphygmomanometer. The homeostasis model assessment of insulin resistance was calculated to determine insulin resistance (IR).**

Results: **TSH level was significantly higher in obese children with MS than that in the others (p = 0.045). Mean TSH level was not different among the BMI-SDS groups (p = 0.590). TSH levels and the fT3/fT4 ratio were not different in children with dyslipidemia, IR or hypertension (p = 0.515, 0.805, 0.973, 0.750, 0.515, and 0.805, respectively).**

Discussion: **obesity severity does not affect TSH level or the fT3/fT4 ratio in obese children and adolescents. IR is in close relationship with TSH level. Elevated TSH level is a risk factor for MS.**

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Key words: *Obesity severity. Thyroid hormones. Metabolic syndrome*.

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LAS RELACIONES ENTRE LAS HORMONAS TIROIDEAS Y LA SEVERIDAD DE LA OBESIDAD, EL SÍNDROME METABÓLICO Y SUS COMPONENTES EN NIÑOS TURCOS CON OBESIDAD

Resumen

Antecedentes: **hemos investigado las relaciones entre la función tiroidea y la severidad de la obesidad, el síndrome metabólico (MS) y los componentes del MS en 260 niños y adolescentes obesos de entre 10 y 17 años de edad.**

Objetivos: **pretendemos determinar la asociación de las funciones tiroideas con la severidad de la obesidad y los componentes del síndrome metabólico (MS) en pacientes pediátricos obesos.**

Métodos: **solo se incluyeron niños y adolescentes obesos, y se dividió a los niños obesos en tres grupos según los cuartiles de índice de masa corporal (BM). El primer cuartil fue el grupo 1, el segundo y tercer cuartil fueron el grupo 2, y el cuarto cuartil fue el grupo 3. El grupo 3 indicó obesidad severa. Los criterios WHO modificados adaptados para los niños se utilizaron para diagnosticar MS. Evaluamos los datos antropométricos y los parámetros del suero bioquímico, incluyendo el perfil lípido y los niveles de glucosa en ayunas (FG), insulina, hormona estimulante del tiroides (TSH), tiroxina libre (fT4) y triyodotironina libre (fT3). Se midió la presión sanguínea (BP) con un *esfigmomanómetro* digital estándar. La evaluación del modelo de homeostasis de la resistencia de la insulina se calculó para determinar la resistencia a la insulina (IR).**

Resultados: **el nivel de TSH fue significativamente mayor en niños obesos con MS que en los demás (p = 0,045). El nivel medio de TSH no fue diferente entre los grupos BMI (p = 0,590). Los niveles de TSH y la proporción fT3/fT4 no fueron diferentes en niños con dislipidemia, IR o hipertensión (p = 0,515; 0,805; 0,973; 0,750; 0,515 y 0,805, respectivamente).**

Discusión: **la severidad de la obesidad no afecta al nivel de TSH ni a la proporción fT3/fT4 en niños y adolescentes obesos. La IR está en relación directa con el nivel de TSH. El nivel elevado de TSH es un factor de riesgo para el MS.**

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Palabras clave: *Severidad de la obesidad. Hormonas tiroideas. Síndrome metabólico*.

Introduction

The prevalence of childhood obesity has increased dramatically worldwide over the past 30 years [1-3]. The prevalence of obesity in Turkish children (3.7–15.4%) parallels that in many other countries[4-7]. This increased prevalence of obesity has led to an increase in the frequency of metabolic syndrome (MS). However, the relationships between thyroid hormone levels and MS, insulin resistance (IR), and other metabolic disorders related to obesity have not been fully explained in children[1, 8]. Thyroid stimulating hormone (TSH), free triiodothyronine (fT3), and free thyroxine (fT4) levels in children with obesity vary from normal to elevated[8]. Thyroid hormones are primarily involved in energy homeostasis, lipid and glucose metabolism, and hypertension. Low fT4 levels are associated with IR and MS, which lead to increased cardiovascular disease risk[9]. Subclinical hypothyroidism (SH) is the beginning stage of overt hypothyroidism and is characterized by a mild increase in TSH in a patient with a normal serum T4 level. TSH has been associated with hyperlipidemia, IR, and obesity in adults[10]. Overt hypothyroidism leads to an increase in plasma total cholesterol (TC) level and blood pressure (BP). Low normal fT4 levels in adults are associated with greater IR, and subjects with low normal thyroid function are at increased risk for cardiovascular disease[11]. The purpose of this study was to examine the associations among thyroid function and obesity severity, MS components and its components in Turkish children and adolescents with obesity.

Methods

This study was conducted retrospectively. All of the clinical parameters and laboratory values were measured at the same time for each paticipiant. A total of 260 obese children 10-17 years of age who were admitted to the School of Medicine at Gaziosmanpaşa University between January 2013 and October 2014 were included in this study. Participants were diagnosed as obese according to body mass index (BMI) SDS, considering the growth curve for each sex and cut-off points proposed by the WHO[12]. Weight was measured using a digital scale (Seca Corp., Chino, CA, USA) with patients wearing light clothing. Height was measured using a portable stadiometer (Seca). BMI was calculated as weight in kg divided by height in meters squared (kg/m^2). A patient was considered obese if their BMI was > 95th percentile[13]. BMI percentile curve for Turkish children was used to determine obesity[14]. Obese children were divided into three groups according to BMI-SDS quartiles. The first quartile was group 1, the second and third quartiles were group 2, and the fourth quartile was group 3. Group 3 indicated severe obesity. BP was measured using a standard digital sphygmomanometer (Omron705IT; Omron Electronics, Ltd., Hoffman Estates, IL, USA) and an appropriate collar according to the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents, considering sex, age, and the height percentile as follows: normal BP (systolic and diastolic BP < 90th percentile), prehypertensive (90–95th percentile), and hypertensive (BP ≥ 95th percentile)[13,15]. Biochemical data were obtained retrospectively from hospital records. Blood samples were collected the morning following a 10–12-h overnight fast to measure serum fasting glucose (FG), TC, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TGs) using enzymatic methods and an autoanalyzer (COBAS 6000; Roche Diagnostics, Indianapolis, IN, USA). Dyslipidemia was defined according to the TC, HDL-C, and TG levels. The TC cut-off value used was the accepted laboratory normal range. The other cutoff values were: HDL < 35 mg/dL, TG > 150 mg/dL, and FG >110 mg/dL. Abnormal glucose homeostasis was determined according to the FG level and the homeostasis model assessment of insulin resistance (HOMA-IR) and the oral glucose tolerance test values. HOMA-IR was calculated according to the Levy formula: FG × fasting insulin/22.5; IR was considered present if the value was > 3.16. The patient was considered to have abnormal glucose homeostasis if FG was > 110 mg/dl or the 120-min glucose level was 140–200 mg/dl[16, 17]. Patients were diagnosed with MS according to the modified WHO criteria for children[18]. Insulin, fT3, fT4, and TSH levels were determined by electrochemiluminescence immunoassay (COBAS C-501&E-601; Roche Diagnostics). Exclusion criteria were hepatic viral infection, alcohol consumption, history of parenteral nutrition, type 2 diabetes mellitus, cushing syndrome, overt hypothyroidism and use of drugs known to affect thyroid function.

MS was defined according to the modified WHO criteria adapted for children. Patients were diagnosed with MS if they met three of the following four WHO criteria: (1) obesity; (2) abnormal glucose homoeostasis; (3) hypertension; and (4) dyslipidemia[19].

Statistical analysis

Data are expressed as mean±standard deviation. Independent sample t test or one way analysis of variances were used to compare the continuous normal data between/among groups. For post-hoc comparisons between the pair-wise groups, the Tukey HSD test was used. Chi-Square test or Yates Correction Chi-square test was used to compare the categorical data between/among groups. Categorical variables were presented as a count and percentage. A p-value <0.05 was considered significant. Analyses were performed using SPSS 19 (IBM SPSS Statistics 19, SPSS inc., an IBM Co., Somers, NY).

Results

The demographic, anthropometric, physical, and biochemical findings for the three groups are shown in table I. Sys tolic BP was significantly higher in group 3 than that in groups 1 and 2 ($p < 0.001$). Diastolic BP was not different among the groups ($p = 0.469$).

No differences in the lipid profile or the TC, TG, LDL-C, or HDL-C levels were observed among the groups. TC, TG, and LDL-C levels were slightly higher in group 3 than those in the other groups, but the differences were not significant. TG and LDL-C levels increased as obesity severity increased. The lowest TC level was observed in group 2. FG levels were normal, and no difference was observed among the groups. Fasting insulin levels were significantly different among the groups ($p < 0.001$). The highest fasting insulin level was detected in group 3. In addition, fasting insulin level increased as obesity severity increased. IR was detected in 148 (%56.9) children and 25 were in group 1, 75 were in group 2, 48 were in grup 3. In group 3 mean HOMA-IR value was significantly higher than that in the other groups ($p < 0.001$). The presence of IR seemed to depend on obesity severity. Children with IR had significantly higher systolic BP, TC and TG levels and they had lower HDL levels than those without IR. While mean systolic blood pressure was significantly different among groups ($p<0.001$), diastolic blood pressure was not different among groups (p:0.469). TSH, fT4 and fT3 levels were similar among the groups. TSH level was slightly higher in group 3 than those in the other groups, but the difference was not significant (p:0.863). The fT3/fT4 ratio was not different among the groups (p:0.569).

The fT3/fT4 ratio was not affected by any of the variables defined in table II. Only the group 3 TC level was negatively correlated with the fT3/fT4 ratio. There is no correlation between severity of obesity and abnormal glucose homeostasis, hypertension, dyslipidemia, or the occurrence of MS. The presence of MS and MS parameters were compared among the groups. The prevalence of MS was 31.5% and abnormal glucose homeostasis (%57.3) was the most frequently seen MS component in the obese children. MS and MS com-

Table I
Demographic, anthropometric and other characteristics of obese children

Variables	*Group1 Mean±SD*	*Group2 Mean±SD*	*Group3 Mean±SD*	*p*
Number (m/f)	65 (38/27)	130 (76/54)	65 (43/22)	
Age (years)	9.78±1.91[a]	12.55±2.31[b]	14.11±1.96[c]	<0.001
Weight (kg)	48.64±9.29[a]	68.9±11.41[b]	91.93±15.59[c]	<0.001
BMI-SDS	2.15±0.44[a]	2.59±0.44[b]	3.09±0.38[c]	<0.001
Systolic blood pressure (mmHg)	105.59±11.51	115.15±13.3	119.62±14.09	<0.001
Diastolic blood pressure (mmHg)	71.59±10.93	73.75±10.85	73.4±10.27	0.469
Total cholesterol (mg/dL)	163.09±33.08	161.49±36.11	167.42±28.56	0.514
Triglycerides (mg/dL)	101.73±41.51	119.91±67.64	120.18±51.86	0.252
LDL-cholesterol (mg/dL)	99.89±30.27	103.49±29.43	108.8±29.80	0.243
HDL-cholesterol (mg/dL)	47.86±11.22	48.46±14.34	46.3±11.26	0.558
Fasting glucose (mg/dL)	83.53±10.32	86.22±10.27	87.14±8.76	0.092
Fasting insulin (μIU/mL)	14.46±8.67[a]	19.61±12.22[b]	26.76±16.02[c]	**<0.001**
AST (U/L)	25.08±8.39	27.4±13.84	26.3±9.50	0.423
ALT (U/L)	20.86±12.95	26.5±27.01	25.31±15.42	0.089
HOMA-IR	2.97±1.73[a]	4.21±2.77[b]	5.75±3.48[c]	**<0.001**
fT3 (pg/mL)	4.06±0.63	4.19±0.73	4.07±0.69	0.428
fT4 (pg/mL)	1.3±0.20	1.34±0.72	1.25±0.18	0.523
TSH (μIU/mL)	2.98±1.19	3.09±1.67	3.1±1.32	0.863
fT3/fT4	3.19±0.49	3.30±0.75	3.31±0.64	0.569

BMI: body mass index, LDL: low density lipoprotein, HDL: high density lipoprotein, AST: aspartate aminotransferase, ALT: alanine aminotransferase, HOMA-IR: homeostais model assesment of insulin resistance, fT3: free triiodothyironine, fT4: free thyroxine, TSH: thyroid stimulating hormone.
**Values are expressed as mean±SD or median[IQR]. For group factor different superscript letters (a,b,c) in the same column (ANOVA) indicate a statistical significant difference.*

Table II
Pearson's Correlations of fT3/fT4 ratio with metabolic variables in groups

	Group1		*Group2*		*Group3*	
	r	*p*	*r*	*p*	*r*	*p*
Age (year)	-0.073	0.612	0.028	0.791	-0.208	0.162
Weight (kg)	0.029	0.844	0.095	0.363	0.111	0.457
BMI-SDS	0.061	0.675	-0.037	0.726	0.233	0.114
Fasting Glucose (mg/dL)	0.257	0.072	0.011	0.916	-0.025	0.867
Fasting Insulin (μIU/mL)	-0.103	0.477	-0.152	0.145	0.085	0.570
OGTT 120min.	-0.114	0.446	-0.085	0.435	0.054	0.731
Diastolic blood pressure (mmHg)	-0.175	0.268	-0.063	0.573	0.047	0.771
Sistolic blood pressure (mmHg)	-0.083	0.592	0.128	0.259	0.111	0.479
Triglyserid (mg/dL)	-0.071	0.626	0.095	0.372	0.054	0.727
HDL- cholesterol (mg/dL)	0.082	0.578	-0.028	0.793	-0.085	0.584
Total- cholesterol (mg/dL)	0.131	0.371	-0.200	0.056	-0.296	**0.045**
LDL- cholesterol (mg/dL)	0.262	0.069	-0.121	0.258	-0.027	0.861
HOMA-IR	-0.029	0.841	-0.142	0.174	0.055	0.712
ALT (U/L)	0.121	0.403	-0.060	0.566	0.004	0.979
AST (U/L)	0.062	0.673	-0.096	0.362	-0.012	0.934

BMI: body mass index, OGTT: oral glucose tolerance test, LDL: low density lipoprotein, HDL: high density lipoprotein, AST: aspartate aminotransferase, ALT: alanine aminotransferase, HOMA-IR: homeostais model assesment of insulin resistance, fT3: free triiodothyironine, fT4: free thyroxine,

ponents' frequency were demonstrated according to groups in table III.

TC, TG and LDL-C levels were significantly higher in obese children with MS than those without MS ($p<0.001$). Fasting insulin and HOMA-IR levels were significantly high in obese children with MS ($p<0.001$). The TSH levels were higher than ≥ 4 mIU/L in 67 patients and 26 (%10) of them had MS. In contrast to the fT3/fT4 ratio, TSH levels were higher in children with MS than in those without. TSH levels and fT3/fT4 ratios of children with IR, abnormal glucose homeostasis, dyslipidemia and hypertansion were not different from those of children without these conditions. According to OGTT results 18 (%6.9) children had impaired glucose tolerance and 8 of them had MS and no one had type 2 diabetes mellitus.

Discussion

Several studies have compared the relationships among thyroid hormones, obesity, and MS in healthy children. However, we investigated the relationships among these parameters according to obesity severity in obese children and adolescents. Obesity is a multi-factorial medical problem triggered by environmental and genetic factors. The main problem is higher dietary energy intake that the body's energy requirement[8]. Childhood obesity is a worldwide health problem, and its prevalence has increased dramatically in the last 30 years[1,10]. Additionally, the prevalence of dyslipidemia, hypertension, IR, and MS has increased with the increase in obesity. Thyroid hormones affect lipid and glucose metabolism, as well as BP, but data regarding

Table III
Frequency of MS and MS components in groups

	Groups			*p*
	Group1 n (%)	*Group2 n (%)*	*Group3 n (%)*	
Abnormal glucose homeostasis	39 (60)	77 (59.2)	33 (50.8)	0.467
Hypertension	50 (82)	90 (83.3)	44 (74.6)	0.374
Dyslipidemia	32 (50)	58 (45.7)	26 (40.6)	0.566
Metabolic syndrome	45 (69.2)	94 (72.3)	39 (60)	0.216

the significance of thyroid function in obese subjects are limited[9,10,20]. Many studies have compared thyroid hormone levels in healthy and obese groups, and their results suggest that TSH levels are significantly higher in obese children than those in healthy children with frequencies of 2–22.2%[21,22]. In the present study, elevated serum TSH levels (≥4 mIU/L) were found in 25.7% of obese children and adolescents, but TSH levels did not increase significantly in parallel with obesity severity. Our results were slightly higher than reported in the literature. This increase in number of elevated TSH levels may be caused from the lack of exculision of Hashimato thyroiditis. Hashimato thyroiditis frequency is higher in obese children than normal weight children. Some investigators have suggested that there is correlations between TSH, thyroid hormones, and BMI, whereas others have found no correlations[23-25]. Lobotkova et al. reported that TSH levels are significantly higher but fT3 and fT4 levels are similar in obese children than in healthy controls[23].

In the present study we found no difference in the fT3/fT4 ratio among our groups. Some investigators have demonstrated that the fT3/fT4 ratio is significantly higher in obese children than that in normal weight children. They claimed that this increase is due to higher conversion of fT3 to fT4 from increased deiodinase activity as a compensatory mechanism for fat accumulation to improve energy expenditure but keep in mind that this hypothesis has not been demonstrated yet[26]. However, we found that the fT3/fT4 ratio did not increase as obesity severity increased. On the other hand fT3/fT4 ratio is in a negative correlation with TC levels. This condition may support this uncorroborated hypothesis forementioned. Spadafranca et al. demonstrated that neither TSH level nor fT3/fT4 ratio increased based on obesity severity in a large obese group[27]. Villa et al. demonstrated that in their study BMI is in a positive correlation with TSH and thyroid volüme in an adult population[28]. Muscogiuri et al. reported that BMI may not reflect the distribution of adipose tissue, and that visceral adipose mass is the best predictor of TSH level[29]. Iodine deficiency is a determinant of elevated TSH level in children with obesity. Many studies that have evaluated TSH and thyroid hormones in obese children did not measure urinary iodine levels[8,10,23]. Free T3 levels in obese subjects are reportedly normal or higher than normal. Lobotkova et al. found that fT3 levels in obese children are similar to those in healthy children[23,30].

We investigated the relationship between thyroid hormone levels and MS and MS components. In the present study 67 obese children's TSH level was ≥4 ng/mL and 26 of them with MS. In contrast to the fT3/fT4 ratio, TSH levels were higher in children with MS than in those without. Previous studies showed that TSH levels are significantly higher in obese adults with MS than in those without[31-33]. According to the HOMA-IR, IR was present in 56.9% of our participants but the TSH level and fT3/fT4 ratio were not different in subjects with or without IR. Many studies support the relationship between insulin sensitivity and thyroid hormones. Small deviations in thyroid hormone levels may result in IR[11]. Owecki demonstrated that TSH level does not influence insulin sensitivity according to the HOMA-IR as in this study[34]. We also found no differences in abnormal glucose homeostasis, hypertension, dyslipidemia, or MS (except IR) among the groups according to the HOMA-IR.

In addition, dyslipidemia was present in 44.6% of the study group in our study, and TSH levels and fT3/fT4 ratio were not significantly higher in dyslipidemic children than in those without although the relationship between TSH level and the lipid profile is well defined[35,36]. Although the results were different in different studies, we could also find elevation of TSH may cause dyslipidemia. Lai et al. found that there is no relationship between dyslipidemia and thyroid hormone levels as in the present study[37]. Our results show that 19.3% of our subjects were hypertensive, and that TSH levels and fT3/fT4 ratio were similar in both children with hypertension and without hypertension. Wang et al. reported that there is no relationship between TSH levels and systolic or diastolic blood pressure[38]. These findings seem to exclude a direct role for blood pressure and dyslipidemia on the central thyrostat and/or on the thyroid hormone secretion and/or on the peripheral conversion from FT4 to FT3.

Conclusion

TSH level may not increase with an increase in obesity severity; however, it may affect the occurrence of MS but not all of the MS parameters. The fT3/fT4 ratio was not related to BMI-SDS, but may be associated with visceral adipose tissue. Further studies with greater power are needed to detect the cause and effect relationship between obesity severity and thyroid function in obese children and adolescents.

Limitation

Thyroid ultrasonography was not performed. Number of elevated TSH levels were slightly high in our study. Visceral adipose tissue was not measured. Thus, we are unsure whether TSH level, the fT3/fT4 ratio, IR, or MS is associated with visceral adipose tissue.

Conflict of interest

The authors declared there is no conflict of interest.

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Drafting the work or revising it critically for important intellectual content; Samet Özer, İlknur Bütün, Ergün Sönmezgöz, Resul Yılmaz, Osman Demir.

Final approval of the version to be published; Samet Özer, İlknur Bütün, Ergün Sönmezgöz, Resul Yılmaz, Osman Demir.

Agreement to be accountable for all aspects of the work; Samet Özer, İlknur Bütün, Ergün Sönmezgöz, Resul Yılmaz, Osman Demir.

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