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Original Article

Thyroid Function in Obese Children and Adolescents and Its Relationships with Metabolic Parameters

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ABSTRACT

Aim: The aim of this study was to evaluate freeT4 and TSH concentrations among children and adolescents with obesity, and to assess possible correlations between glucose and parameters of lipid metabolism.

Materials and Methods: A retrospective analysis of 100 obese patients, aged between 8-18 years, was performed in the pediatric endocrinology outpatient clinic. The anthropometric measurements, free T4 and TSH concentrations, glucose levels and lipid profile of children and adolescents with obesity were determined.

Results: Mean age of patients was 11.43 ± 2.64 years. Fasting blood glucose and cholesterol levels had a significant positive correlation with TSH levels, and multiple regression analysis revealed that 1 unit of increase in blood glucose and cholesterol increased TSH levels by 0.047 units and 0.012 units, respectively.

Conclusion: There is still a lack of data regarding the relationship between thyroid function and other metabolic risk factors in children with obesity. Our findings add to the literature in terms of demonstrating that obesity may have a central effect on thyroid function, before any effects on insulin levels and anthropometric features become apparent. It is important to better understand the relationship between thyroid function and obesity in order to develop strategies to prevent or treat childhood obesity.

Keywords: Childhood obesity, thyroid hormone, glucose levels, lipid profile

Introduction

Childhood obesity has become one of the most important health problems in the world (1). As the prevalence of obesity increases, so does the prevalence of comorbidities associated with obesity which comprise a rather long list, including abnormalities in the endocrine, cardiovascular, gastrointestinal, pulmonary, orthopedic and neurologic systems, as well as important psychological and social problems. Some comorbidities such as type 2 diabetes mellitus and steatohepatitis are extremely common in obese children, while thyroid dysfunctions are also frequently observed (2, 3). Recently there has been increased interest in the association between thyroid dysfunction and obesity (4-6). The mechanisms underlying the thyroid hormone changes in obesity are unclear, but several mechanisms have been proposed in the literature describing the different forms of thyroid dysfunction in obese people which may be listed as follows: subclinical hypothyroidism due to iodine deficiency, autoimmune thyroiditis and thyroid-stimulating hormone (TSH) receptor gene mutation, functional disorders in the hypothalamus-pituitary-thyroid axis, thyroid hormone resistance, mitochondrial dysfunction, production of Leptin-mediated pro-Thyrotropin-releasing hormone (TRH) (7, 8). It is quite well known that, thyroid hormones are effective on regulation of energy homeostasis, fat oxidation, and lipid and carbohydrate metabolism. Therefore, it is considered that increased TSH levels are indicative of the changing energy balance in obesity (9, 10).

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In many studies, high TSH levels have been associated with high triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC) levels, insulin resistance and risk of coronary disease in obese children (11, 12). However, it is unclear whether obesity and TSH levels have an 'adaptive association'; whether metabolic rate is increased in order to decrease weight gain, whether there is an increase in subclinical hypothyroidism or thyroid resistance, and therefore, whether obesity contributes to the dysfunctions in glucose and/or lipid metabolism, or is a by product of increased weight.

There are few studies that have focused on the relationship between obesity and thyroid function in Turkish children and adolescents (13-16). Furthermore, data is limited regarding the relationship between thyroid function and other metabolic risk factors in children with obesity. The aim of this study was to evaluate free thyroxin (fT4) and TSH concentrations among children and adolescents with obesity, and to assess possible correlations between glucose and parameters of lipid metabolism.

Materials and Methods

A retrospective analysis of 100 obese patients, aged between 8-18 years was performed in the pediatric endocrinology outpatient clinic between 01 September 2018 and 20 December 2018.

Ethical approval was obtained from our faculty ethical committee (Baskent University Institutional Review Board number KA19/27). The current study was conducted according to the principles put forth by the Helsinki Declaration and Good Clinical Practice guidelines.

Subjects with chronic medications, those who declined to take part, those with underlying chronic disease, and patients who were diagnosed with syndromic obesity were excluded from the study.

Anthropometric data, including weight, weight standard deviation score (SDS), height, height SDS, body mass index (BMI) and BMI SDS, were recorded for all subjects. All anthropometric data were converted to standard deviation scores using Turkish standard data (17). Subjects with BMI SDS>2 were regarded as obese.

The blood samples, for the measurement of thyroid hormones (TSH, fT4), lipid profile, and glucose and insulin, was obtained from all patient. All blood specimens were collected in the morning between 08:00 and 10:00 after 10-hour fasting. Insulin measurement (IRI) was performed using the chemiluminescence method on an Advia Siemens Centaur XP device (Ireland). Fasting blood glucose was measured using the spectrophotometric method on an Advia Siemens 1800 (Japan) device. Homeostatic Model Assessment – Insulin Resistance (HOMA-IR) was calculated using the following formula: fasting plasma glucose (mmol/l) x fasting insulin (mUI/l) / 22.5 (18). TSH (reference range: 0.27-4.2 µIU/ml) and fT4 (reference range: 11-26 pmol/l) concentrations were measured via chemiluminescence methods with the use of an Abbott Architect i4000 (USA) device. TC (mg/dl), high-density lipoprotein cholesterol (HDL-C, mg/dl), LDL-C (mg/dl) and TG (mg/dl) concentrations were measured through photometric methods via an Abbott Architect c8000 (USA) device.

Statistical Analysis

Statistical analysis was performed on SPSS version 21 (SPSS Inc., Chicago, IL). For the normality check, the Shapiro Wilk test was used. Pearson and Spearmen Correlation Coefficients were calculated (in accordance with normality of distribution) for determining relationships between variables. Multiple linear regression analysis with stepwise selection method was used for more reliable assessment of the relationships between TSH and fT4, and gender, age, anthropometric measurements, carbohydrate and lipid parameters related to obesity. A p values less than 0.05 were considered to show statistically significant relationships.

Results

One hundred (57 girls, 43 boys) children and adolescent cases with obese were included in the study. Mean age of the subjects was 11.43 ± 2.64 years. Descriptive statistics of our variables are given in Table I.

Table I. Main anthropometric, biochemical and hormonal parameters in obese patients

	Mean±SD
Age (yr)	11.43±2.64
Weight (kg)	65.37±16.47
Weight SDS	2.76±0.70
Height (cm)	149.21±13
Height SDS	0.69±1.20
BMI SDS	2.60±0.40
fT4 (pmol/l)	14.45±1.97
TSH (µIU/ml)	3.60±1.79
Glucose (mg/dl)	88.27±6.69
Insulin (mUI/l)	15.02±6.95
HOMA-IR	3.29±1.63
Total cholesterol (mg/dl)	167.77±31.47
HDL-cholesterol (mg/dl)	47.96±9.48
LDL-cholesterol (mg/dl)	101.54±26.92
Triglyceride (mg/dl)	121.72±47.33

BMI: Body mass index, SDS: Standard deviation score, fT4:Free thyroxin, TSH: Thyroid-stimulating hormone, HOMA-IR: Homeostatic Model Assessment – Insulin Resistance

The relationships between fT4 and TSH values and other parameters measured in the study, found that no significant correlations for fT4, whereas fasting glucose (r=0.265; p=0.008), (Figure 1) and cholesterol (r=0.220; p=0.028), (Figure 2) levels were significantly and positively correlated with TSH values (Table II).

A multiple linear regression analysis with fT4 as a dependent variable was performed, but none of our independent variables demonstrated a significant result. On the other hand, fasting glucose and cholesterol were found to be significant independent variables when TSH was defined as the dependent variable. The multiple linear regression model was: TSH = 0.047 * fasting glucose + 0.012 * Cholesterol - 5.008 (p=0.002); meaning that, 1 unit of increase in fasting glucose increases TSH by 0.047 units, while 1 unit of increase in cholesterol increases TSH by 0.012 units (Table III).

Discussion

In the current study, we found that TSH levels were positively correlated with blood glucose and total cholesterol levels in a group of obese pediatric patients who were

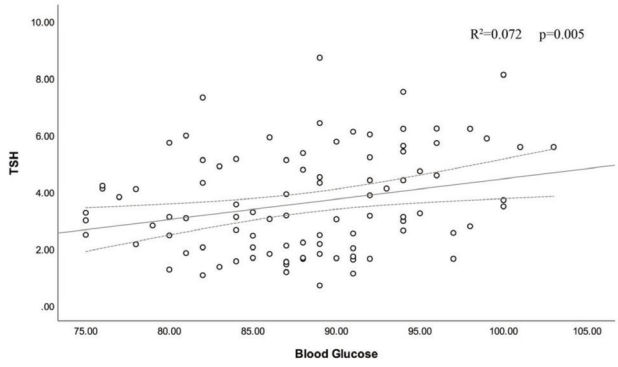

Figure 1. Scatter plot of TSH and blood glucosekidney was measured (D) of kidney was measured

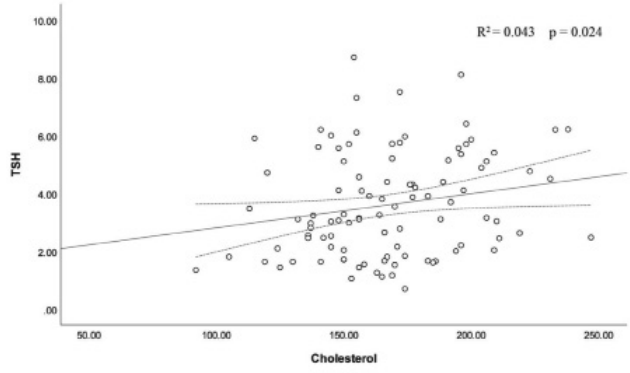

Figure 2. Scatter plot of TSH and Cholesterol

Table II. Relationships between various parameters and the levels of fT4 and TSH

		Age	Weight	Weight SDS	Height	Height SDS	BMI SDS	Glucose
fT4	R	-0.036	-0.148	-0.088	-0.112	-0.015	-0.141	0.003
	P	0.719	0.143	0.382	0.267	0.883	0.160	0.978
TSH	R	0.146	0.143	0.113	0.092	-0.057	0.112	0.265
	P	0.147	0.156	0.263	0.361	0.576	0.269	0.008*
		Insulin	**HOMA-IR**	**Cholesterol**	**HDL**	**LDL**	**Triglyceride**	
fT4	R	-0.119	-0.126	0.008	-0.063	0.096	-0.115	
	P	0.237	0.212	0.934	0.533	0.343	0.253	
TSH	R	0.141	0.195	0.220	0.015	0.183	0.165	
	P	0.163	0.051	0.028*	0.885	0.069	0.100	

*Statistically significant correlation, fT4: Free thyroxin, TSH: Thyroid-stimulating hormone, BMI: Body mass index, SDS: Standard deviation score, HOMA-IR: Homeostatic Model Assessment-Insulin Resistance

Table III. Multiple Linear Regression Analysis Results with TSH as a Dependent Variable

	β	Std. Error	t	p	95.0% CI for β	
					Lower	Upper
(Constant)	-5.008	2.469	-2.028	0.045	-9.909	-0.107
Fasting Glucose	0.074	0.026	2.898	0.005	0.023	0.125
Cholesterol	0.012	0.005	2.29	0.024	0.002	0.023

TSH = 0.047, * Fasting Glucose + 0.012, * Cholesterol - 5.008
n = 100, R^2=0.119, F=6.561, p=0.002

otherwise healthy, Furthermore, multiple regression analysis revealed that TSH levels were directly affected by the levels of fasting glucose and cholesterol. However, fT4 levels were not associated with any of the parameters measured. Although we did not investigate causal relationships, the fact that TSH levels were associated with glucose and cholesterol levels while fT4 levels were not, may indicate that obesity has an initial effect on central thyroid function, which may lead to development of metabolic pathologies.

In recent years, the effects of thyroid hormones on energy balance and adipose tissue have been frequently studied. Many recent cross-sectional studies reported the presence of associations between thyroid hormones and obesity (4, 5, 19-23). The levels of cyclic AMP, which is a second messenger for many hormones including TSH and TRH, is closely associated with energy balance and the production/use of ATP. The correlation between TSH and blood glucose levels may indicate a complex relationship in terms of energy production and thyroid levels. Although TSH increase may be a simple response to increased glucose, aimed at regulating metabolism to compensate for and utilize the ATP-producing glucose in tissues, there may also be a more complex explanation: considering the insulin resistance of obese patients, ATP depletion may develop in cells, leading to a decrease in the production of the second messenger c-AMP by adenylate cyclase. Liver cells are one of the main targets of thyroid hormones, and with depletion of cyclic AMP, the action of these hormones in hepatocytes would be affected. The clinical result would be hepatocyte unresponsiveness to thyroid hormones and an increase in TSH levels could be required to overcome this decrease. These may be the first steps of a progressive series of events that would lead to TSH resistance (24, 25). In another studies of obese children show that only a minority suffer from autoimmune thyroiditis, while most demonstrate moderately increased TSH levels without thyroid disease (10, 26). Likewise, Dekelbab et al.(27), reported that higher prevalence of mild elevation of TSH values, in the absence of autoimmune thyroid disease, in a group of obese children compared to normal-weight control groups. Stichel et al.(28), in their study, determined that in childhood obesity TSH and T3 levels are significantly increased; in most cases, however, these increases are not explained for by thyroid autoimmunity or iodine deficiency. Consequently, further controlled studies are required to explain our findings–which are far from conclusive– given that many other factors (e.g. iodine deficiency, thyroid autoimmunity) that may alter thyroid levels were not evaluated in our study.

Some studies have reported that TSH levels in obese individuals are slightly higher than those in normal weight subjects and TSH levels are positively associated with BMI and weight change (10, 29). Reinehr et al.(30), found that peripheral thyroid hormones (T3, T4) and TSH levels were moderately increased in obese children. In our study, no significant correlation was found between TSH elevation and BMI (or any other anthropometric measurement). However, we found a significant positive correlation between TSH and cholesterol levels. Multiple regression also showed that 1 unit of increase in cholesterol level translated to a 0.012-unit increase in TSH levels. There are a number of studies on the association between thyroid function and lipid profiles in obese and overweight children, but the results are variable (31). Grandone et al. (20), revealed that TSH levels had no relation to HDL-C and triglycerides. However, similar to our findings, Aeberli et al.(12), demonstrated that TSH levels in obese children had a significant positive correlation with total cholesterol and LDL-C.

In our study, we determined a significant positive correlation between TSH and fasting glucose levels, which was also apparent in multiple regression analysis; a 1-unit increase in fasting glucose was found to cause an increase of 0.047 units in TSH. However, when we evaluated relationships between HOMA-IR and insulin levels with that of fT4 and TSH, we found no significant correlations. Although experimental studies have shown that thyroid hormones may impact insulin sensitivity by influencing expression or activation of uncoupling protein, β adrenergic receptor and peroxisome proliferator-activated receptor-γ (32), our findings may suggest that TSH levels (and therefore thyroid function) are affected much earlier than insulin. If so, then it is plausible that the early TSH changes are in fact a contributor to the insulin resistance seen in obese patients. Future studies would benefit from long-term follow-up of thyroid and insulin levels in children with obesity in order to elucidate which causes the other, or to determine whether a causal relationship exists between these two crucial parameters of human metabolism.

Hyperthyroidism and hypothyroidism may cause impaired glucose tolerance of the liver, muscles and adipose tissues (33). Several studies have examined the relationships between thyroid function and insulin resistance in children and adults, but there are conflicting findings regarding the association of insulin resistance with hypothyroidism or hyperthyroidism (34). Maratou et al.(35) determined that insulin resistance was comparable in patients with both hypothyroidism and subclinical hyperthyroidism. However, there are several reports of associations between hypothyroidism and insulin resistance in adult patients, which later progressed to metabolic syndrome (36, 37).

The limitations of our study include the absence of a control group; however, our aim was to assess the relationships of measured parameters in obese children and adolescents. Therefore, our analyses are not necessarily affected by the lack of a control group. Nevertheless, a control group would have provided a chance to observe the differences in the relationships among parameters (or lack

thereof) between those with and without obesity, and this must be noted as a limitation. Secondly, this is a retrospective single-center study and carries all the restrictions associated with such studies. Lastly, we could not analyze various other factors that may have affected thyroid levels such as iodine deficiency, autoimmune thyroiditis.

Conclusion

In the current study we aimed to determine fT4 and TSH concentrations among children and adolescents with obesity and to assess possible correlations between various parameters, including anthropometric measurements, glucose levels and lipid profile. Fasting blood glucose and cholesterol were positively correlated with TSH, while none of the parameters were associated with fT4 levels. We believe our findings add to the literature in terms of demonstrating that obesity may have a central effect on thyroid function, before any effects on insulin levels and anthropometric features become apparent. Considering that the physiopathology of thyroid function changes in childhood obesity and the effects of thyroid function on lipid and carbohydrate metabolism are still controversial, we believe future studies are warranted in order to better understand the relationship between thyroid function and obesity.

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