ASSOCIATIONS OF THYROID VOLUME AND FUNCTION WITH CHILDHOOD OBESITY

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Context. The links between obesity and thyroid function or thyroid volume in children are still controversial with limited available data.

Objective. This study aimed to examine thyroid function and volume in obese Turkish school-age children in comparison to normal-weight children.

Design. Cross-sectional study.

Subjects and Methods. One hundred obese children (47 boys, 53 girls; mean age 10.34 ± 2.79 years) with a body mass index (BMI) above 95th percentile, and 100 normal-weight children (42 boys, 58 girls; 10.34 ± 2.79 years) were included. The study parameters were BMI z score (Z-BMI), body surface area (BSA), thyroid volume, free thyroxine (fT4) and thyroid stimulating hormone (TSH) levels.

Results. The mean TSH and fT4 levels did not show a significant difference between obese and normal-weight children ($p > 0.05$). The mean thyroid volume was higher in obese children (6.46 ± 5.84 and 4.64 ± 1.44 , respectively; $p = 0.043$). fT4 correlated negatively with Z-BMI in both normal-weight and obese children ($r = -0.285$, $p = 0.004$ and $r = -0.289$, $p = 0.004$, respectively). Thyroid volume, on the other hand, correlated positively with Z-BMI, again in both normal-weight and obese children ($r = 0.657$, $p < 0.001$ and $r = 0.444$, $p < 0.001$, respectively). Similar associations were found for BSA.

Conclusions. Thyroid volume correlated positively and fT4 correlated negatively with Z-BMI and BSA, in both obese and normal-weight school-age children, whereas TSH appears to be independent of these parameters.

Key words: thyroid function, thyroid volume, childhood obesity.

INTRODUCTION

Globally, obesity is a well-recognized public health problem affecting both adults and children (1). The prevalence of obesity in children increased worldwide by 47.1% between 1980 and 2013, which

varies between geographic regions and countries (2). In Turkey, although data from nation-wide studies is not available, the prevalence of obese school-aged children has been reported to be between 9% and 27% in regional studies (3, 4). Obesity may be associated with hormonal changes such as decreased growth hormone (GH) and increased insulin-like growth factor-1 (IGF-1) secretions, both of which are closely associated with alterations of insulin resistance (5, 6). Alteration of GH/IGF-1/insulin axis by obesity may be associated with the development of metabolic syndrome; and thus with increased risk of developing diabetes and cardiovascular disease, leading to increased morbidity and mortality during both childhood and adult life (5, 7).

On the other hand, the link between obesity and thyroid function has remained controversial. Some studies showed a subclinical hypothyroidism in overweight or obese children with slightly raised thyroid stimulating hormone (TSH) and normal free thyroxine (fT4), which appears to be an adaptive response rather than a cause of obesity (8-10). Other studies found inconsistent results with increased, decreased or normal levels of thyroid hormones in obesity (11, 12). The altered thyroid function in obesity seems to revert to normal without any treatment, only by weight loss, irrespective of how the weight loss occurs. This suggests that the abnormal thyroid function is a consequence rather than a cause of obesity (13). Like thyroid hormonal changes, alterations in thyroid volume can also be seen in childhood obesity. WHO recommended normative values or upper limits for thyroid volume in children between 6-15 years of age with sufficient or depleted iodine intake, respectively (14). However, there are relatively few and controversial data about the association of thyroid volume and obesity in children and adults (8).

In our study, we aimed to compare the thyroid function and volume in a cohort of obese and morbidly obese Turkish school-age children against normal-weight children of the same age.

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MATERIAL AND METHODS

Study design and population

This cross-sectional descriptive study included 200 Turkish school-aged children (age range, 6-15 years; 89 boys, 111 girls) who were admitted to the pediatric outpatient clinic in our hospital between January 2014 and December 2014. The study population was divided into two groups based on the chart of body mass index (BMI) percentiles derived for Turkish children with normal iodine intake. The first group (study group) consisted of 100 obese and morbidly obese children (47 boys, 53 girls) who had a BMI above the 95th and 99th percentile, respectively, and the second group (the control group) consisted of 100 children (42 boys and 58 girls) who were below the 85th percentile in this chart with the majority falling between 25-50th percentile. Children in the study group were admitted to our hospital for obesity follow-up and children in the control group for routine pediatric check-up examinations. Children in whom obesity could be attributed to genetic factors or chronic endocrinological disorders were excluded from the study.

The study was approved by the Institutional Ethics Committee and conducted in accordance with the latest version of Helsinki Declaration. Informed consent was obtained from the parent of each child.

Study parameters

The study parameters were z score for body mass index (Z-BMI), body surface area (BSA), fT4, TSH and thyroid volume. On admission of a child to our hospital, demographics including weight and height were recorded. Z-BMI was calculated using the following formula: (observed BMI of the child – mean BMI of the study population) / standard deviation of BMI in the study population. BSA (m²) was calculated using the Dubois formula (15): weight (kg) 0.425 X height (cm) 0.725 X 71.84 X 10⁻⁴. Venous blood was collected from each subject following a 12-hour fasting and abstinence from intensive physical activity. Samples were stored at -80 C until measurement. TSH and fT4 were measured using an electrochemiluminescence and a chemiluminescence immunoassay kit, respectively (Roche Diagnostics GmbH, Mannheim, Germany). Reference range for fT4 and TSH was 2.50-5.60 ng/dL and 0.51-4.84 μ IU/mL, respectively. The intra-assay coefficient of variation was <6%, and the inter-assay variation coefficient was <10%.

The thyroid volume was measured by the ultrasonography equipment Toshiba Applio 400

(Tokyo, Japan) using linear 14-18 MHz probes whereby all the patients were examined in supine position with an extended neck. The examinations were focused only on the assessment of the thyroid volume, so any parenchymal abnormalities or lesions were neglected for the purpose of the study. Thyroid volume was obtained by adding the volumes of two lobes which was calculated by the formula of anteroposterior dimension (cm) X mediolateral dimension (cm) X craniocaudal dimension (cm) X 0.5 as suggested by Brunn *et al.* (16).

Statistical analysis

All statistical analyses were performed using Number Cruncher Statistical System (NCSS) 2007 (Kaysville, Utah, USA). The study data were summarized with descriptive statistics (e.g. mean $\pm$ standard deviation, frequency (percentage)). The mean Z-BMI, BSA, thyroid volume, fT4 and TSH of the groups were compared. The correlations between Z-BMI/BSA and thyroid volume/thyroid function (TSH and fT4) were analyzed within each group. Pearson's chi-squared test was used for the comparisons between categorical data and Mann Whitney U test was used to compare continuous variables. For correlations between parameters, Spearman's correlation analysis was done. A p value <0.05 was considered statistically significant.

RESULTS

Demographics and anthropometric measurements

The study and the control groups were comparable with respect to age, gender and height ($p>0.05$). However, mean weight, Z-BMI and BSA of the study group were significantly higher than those of the control group ($p<0.001$ for all comparisons) (Table 1).

Thyroid function and thyroid volume

Although mean TSH and fT4 levels did not show a statistically significant difference between the study group and the control group ($p>0.05$), the mean thyroid volume was higher in the study group (6.46 ± 5.84 vs. and 4.64 ± 1.44 mL, respectively; $p=0.043$) (Table 2).

Correlation of thyroid function and thyroid volume with Z-BMI and BSA

fT4 correlated significantly and negatively with Z-BMI in both the study and control group ($r=-0.289$, $p=0.004$ and $r=-0.285$, $p=0.004$, respectively)

(Table 3). Z-BMI was significantly and positively correlated with thyroid volume in both the study group ($r=0.444$, $p<0.001$) and the control group ($r=0.657$, $p<0.001$) (Table 3). There was no correlation between TSH and Z-BMI in either of the groups (Table 3). Similar associations were found for BSA (Table 3).

DISCUSSION

In this cross-sectional observational study, we primarily found that thyroid volume of obese children was higher than normal-weight children of the same age, whereas TSH and fT4 levels did not differ significantly

between these two groups. We also found a positive correlation between Z-BMI and thyroid volume and a negative correlation between Z-BMI and fT4 levels, in both obese and normal-weight children.

Various studies on the correlation between obesity and changes in thyroid function in children have been conducted. In most of them, TSH has been consistently found higher in obese children than in non-obese, which may be explained by an increased pituitary and peripheral resistance in obese children to circulating thyroid hormones (T3), resulting from an impaired negative feedback between TSH and thyroid hormones (17). Chen *et al.* (5) found that thyroid

Table 1. Demographic and anthropometric characteristics of study patients

	Study group Obese children (n=100)	Control group Normal-weight children (n=100)	p
Age, y	10.3±2.8	10.4±2.8	0.860
Female gender, n (%)	53 (48.2%)	55 (55.0%)	0.447
Weight, kg	58.5±18.7	38.1±13.9	<0.001
Height, cm	144.2±15.6	144.9±15.7	0.793
Z-BMI	-0.8±0.5	0.8±0.6	<0.001
BSA, m ²	1.5±0.3	1.2±0.3	<0.001

Unless otherwise stated, data presented in mean±standard deviation. Z-BMI, z score for body mass index; BSA, body surface area.

Table 2. Thyroid function and thyroid volumes of study groups

	Study group Obese children (n=100)	Control group Normal-weight children (n=100)	p
TSH, μ IU/mL	2.9±1.3	2.6±1.0	0.246
fT4, ng/dL	1.1±0.1	1.1±0.1	0.703
Thyroid volume, mL	6.5±5.8	4.6±1.4	0.043

Data presented in mean±standard deviation. TSH, thyroid stimulating hormone; fT4, free thyroxine.

Table 3. Correlations of Z-BMI and BSA with TSH, fT4 and thyroid volume

		Study group Obese children (n=100)	Control group Normal-weight children (n=100)
Correlations with Z-BMI			
TSH	r	-0.043	0.177
	p	0.668	0.077
fT4	r	-0.289	-0.285
	p	0.004	0.004
Thyroid volume	r	0.444	0.657
	p	<0.001	<0.001
Correlations with BSA (m²)			
TSH	r	0.069	0.165
	p	0.498	0.101
fT4	r	-0.340	-0.322
	p	0.001	0.001
Thyroid volume	r	0.521	0.696
	p	<0.001	<0.001

r, Spearman's correlation coefficient; TSH, thyroid stimulating hormone; fT4, free thyroxine; BMI, body mass index; Z-BMI, Z score for body mass index; BSA, body surface area.

function including fT3, fT4 and TSH and thyroid volume were significantly different among the three groups of 242 overweight, 212 normal-weight, and 327 of obese children with a mean age of 11 years. Subclinical hypothyroidism was found in 28 normal-weight, 36 overweight, and 53 obese children. The authors found associations of thyroid function and thyroid volume with obesity in their study and observed that the change in thyroid function and morphology was significantly related to BMI. They concluded that obese children could show a different degree of thyroid impairment that was related with obesity-associated low-grade inflammation (5). Increased levels of TSH have also been attributed to this inflammatory state seen in obesity (17). Reinehr (8) and Lobotkova *et al.* (11) also found higher prevalence of increased TSH levels in obese children. Other studies with obese children also showed elevated TSH levels (18-20). However, our study found that TSH levels in the obese group did not differ significantly from the control group.

Free T3 and T4 levels in obese children have also been investigated in many studies. The results of these studies were mostly inconsistent. Some did not find a significant change in fT3 and fT4 in obese children (8, 11, 21). However, some demonstrated normal or slightly increased levels of T3 and T4 in obese children (13, 18-20, 22-24). It has been suggested that these increases in T3 and T4 may represent an adaptation process to weight gain in an attempt to increase the energy expenditure and basal metabolic rate (17). Conversely, in a study conducted by Radetti *et al.* (18), decreased levels of T3 and T4 were reported in obese children. These inconsistent findings about thyroid hormones may be attributed to low sample sizes in the studies precluding accurate and reproducible assessment of the changes in thyroid functions. Larger study populations may be needed to obtain more consistent results. In the present study, we could not show any statistically significant difference in fT4 between obese children and the control group.

BMI is considered as an indicator for general obesity; therefore, it has been used in many studies investigating the correlation of obesity and thyroid hormones. A large population-based study led by Chen *et al.* (5) found positive correlations between BMI and T3/T4 levels, which was confirmed in other studies (25-27). A positive correlation between BMI and TSH levels was also demonstrated (5, 25-27). In our study, there was a negative correlation between Z-BMI and fT4 in both obese and normal-weight children.

Thyroid hormones regulate energy expenditure

and appetite (17). Obesity alters hormonal balance in general; and thyroid hormone levels are also affected. It has been suggested that leptin may play a role as a link between obesity and thyroid hormones. Leptin is a fat tissue hormone secreted by adipocytes and is thought to affect body weight regulation by acting on the hypothalamus leading to decreased appetite and lower food intake, and increased energy expenditure (28). Leptin acts on the hypothalamus-pituitary axis to secrete thyroid releasing hormone (TRH) and TSH, which stimulate adipogenesis via inducing differentiation of preadipocytes into adipocytes and T4 formation (17). Adipocytes in turn secrete more leptin; so a vicious cycle forms. Therefore, increased levels of leptin are positively correlated with body mass adiposity (28-30). Paradoxically, leptin also inhibits thyroid hormone secretion from thyrocytes and increases resistance to thyroid hormones (28). Though the relationship between leptin and thyroid hormones is yet not clear, leptin levels in thyroid dysfunction tend to change parallel to the changes in weight. Thus, in primary hypothyroidism, low levels of thyroid hormones and high TSH appear to be associated with elevated leptin levels and increased resistance to thyroid hormones, leading to an increase in BMI (28). So obesity seems to be associated with high leptin levels and high receptor resistance (28). The resulting vicious circle may only be interrupted by a reduction of the adipose tissue mass.

Studies showed that regardless of how the weight loss occurs, thyroid hormones seem to revert to normal levels. In a longitudinal study on a large study group, Santos *et al.* (31) showed that following the weight loss by any way, TSH levels return to normal ranges without additional treatment. Other studies reported similar results (12, 13, 20, 24-26). Decreased levels of T3 and T4 after weight loss were also reported in many studies (17, 24, 26, 32). Only few studies could not demonstrate any change in TSH levels after weight loss (22).

Relatively few studies have been conducted on the relationship between thyroid volume and obesity in adults and in children. Sari *et al.* (33) investigated this association in obese women and found a positive correlation between TSH, thyroid volume and BMI (33). Chen *et al.* (5) investigated the changes of thyroid structure and volume in 880 children and adolescents of which 327 were obese. Consistent with the literature, our study also showed a positive correlation between Z-BMI and thyroid volume both in obese children and the control group. We also found that thyroid volume is inversely correlated with fT4. The reason for increasing

thyroid volumes with increasing BMI is not clear. It has been suggested that obesity could be associated with a chronic low-grade inflammation where high-sensitivity CRP has been shown to correlate with BMI (5, 34). Other inflammatory markers (cytokines) including interleukin-1, interleukin-6 and tumor necrosis factor- α have also been shown to increase in obesity. It has been suggested that these cytokines may block sodium iodide symporter mRNA expression and iodine-uptake in human thyroid cells which in turn increases endothelial permeability and causes a local vasodilation (5, 17, 35, 36). All these events might account for the positive correlation between thyroid volume and BMI. Some studies also report a hypoechoic parenchymal pattern suggestive of Hashimoto's thyroiditis seen on ultrasonography examination of obese children which may represent these low-grade inflammatory changes. This hypoechogenicity appears to precede overt Hashimoto's thyroiditis (5, 37). However, unlike in Hashimoto's thyroiditis, no increase in antithyroid antibodies was detected in these patients. It has also been reported that following weight loss normal homogeneous sonographic pattern was restored (17).

Our study should be interpreted within its limitations. Firstly, we did not evaluate inflammatory markers and leptin levels to substantiate the hypothetical links between obesity, thyroid function and thyroid volume. Secondly, one important study parameter would have been the iodine status, for example urinary iodine levels, since iodine levels may be associated with thyroid volume. Thyroid volume has been shown to increase in association with inadequate or excess iodine intake, where urinary iodine concentration between 100 and 299 $\mu\text{g/L}$ was defined as adequate iodine intake (38, 39). In addition, this study did not evaluate thyroid parenchyma on ultrasound examination but focused only on volumetric measurement of the gland. Likewise, thyroid peroxidase antibodies were not assessed for the presence of autoimmune thyroiditis. Both inflammatory conditions may play a role on the volume changes of the gland. A relatively low sample size may be considered another limitation of this study. Further studies with larger sample size and more parameters may be needed to clarify these associations and to better assess these inconsistent changes of thyroid function reported in the literature.

In conclusion, findings of the present study suggest that thyroid volume correlates positively and fT4 correlates negatively with Z-BMI and BSA, in both obese and normal-weight school-age children, whereas TSH appears to be independent of these parameters.

Conflict of interest. The authors declare that they have no conflict of interest concerning this article.

Author contributions. LS and ZEO conceptualized the study and LS, HEO, CN contributed to design, LS and HEO recruited patients and performed study procedures and ZEO, LS, and CN contributed to analysis and interpretation of data, LS wrote the manuscript and all other authors critically reviewed and approved the manuscript.

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