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Compare the Relative Frequency of Thyroid Function Disorders in Obese and Overweight Children with Non-Obese Children; a Case-Control Study

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Abstract

Background

Childhood obesity has become a global epidemic. In the recent studies has reported risk of thyroid dysfunction due to obesity. Therefore, this study intends to compare the relative frequency of thyroid function disorders in obese and overweight children with non-obese children.

Materials and Methods

This case-control study during 2015 to 2016 in Birjand- Iran was done on 137 children and adolescents (6 to 18 years), with overweight and obesity as case group and 137 non-obese subjects as control group. Body mass index (BMI), thyroid stimulating hormone (TSH), free triiodothyronine (FT3) and free thyroxine (FT4) were measured, and analyzed using SPSS software version19.

Results

TSH level in obese children was significantly more (P<0.001), and FT4 (P<0.001) and FT3 levels (P=0.003), less than non-obese subjects. In the control group, 0.73% and in the case group, 2.92% of patients showed hypothyroidism disorder, that difference was not significant (P=0.177). In the control group, there was significant relationship between TSH with FT4 (P <0.001) and FT3 (P <0.001). Moreover, in the case group, there was significant relationship between TSH with FT4 (P <0.001) and FT3 (P = 0.001), and also, between FT4 with FT3 (P <0.001).

Conclusion

Overweight and obesity in children and adolescents can be effect on increase of TSH and decrease of FT4 and FT3. Long-term studies with larger sample size is suggested.

Key Words: BMI, Children, Obesity, Overweight, Thyroid function disorders.

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1- INTRODUCTION

In the recent decades, a significant increase in the prevalence of obesity and overweight in children and adolescents have been reported. The most important behavioral factors underlying obesity are sedentary life and high-calorie diet. In the recent decades, due to lifestyle changes, childhood obesity has become a global epidemic (1-3). The prevalence of childhood obesity is also growing rapidly in Iran, which could be caused by changes in lifestyle (4-5). Overweight and obesity prevalence rates are varied across Iran and high in certain regions (4, 6). Childhood obesity increases risk of diabetes and cardiovascular disease (CVD), such as blood lipid abnormalities, hypertension, atherosclerosis, and the increase risk of obesity in adulthood (7-11). The importance of obesity in childhood and adolescent is not only due to physical and psychological effects of premature, but also due to increase adulthood obesity, morbidity and mortality and high economic costs on society (12-14).

Previous studies have reported that hypothyroidism caused by abnormalities in food metabolism, will lead to fat build up, and eventually cause thyroid obesity. Current studies however, talk about how obesity alone, might lead to thyroid dysfunction. The structural changes and thyroid activities common in obese children can serve as an evidence. These studies show the prominent link between body mass index and the thyroid hormones levels. Also, increase of body fats can be effective in the thyroid structure changes. The results of studies also show that thyroid function returns to normal after weight loss. In these researches, the conversion of thyroid dysfunction in childhood into chronic thyroid diseases in adulthood has not been proven (15). Most researches in adults have investigated the relationship between body mass index (BMI) and abnormal thyroid function (16-18). Low thyroid hormone is associated with decreased energy expenditures (19) and fluid retention (20) in adults with obvious hypothyroidism. However, in several studies pay special attention to thyroid function in obese children; because is thought that one of the causes of obesity is hypothyroidism, and thyroid function tests are still one of the most common experiments that measured in this group of patients (21). Many studies have demonstrated that thyroid stimulating hormone (TSH) level in obese children is higher than the non-obese children and the increase is not a risk factor for metabolic diseases (15, 21). In some studies, have been shown weight losses associated with reducing TSH (22).

In some researches of euthyroid range and adverse outcomes in adults with obesity, high adiposity is associated with increased thyroid stimulating hormone (TSH) (17, 18, 23, 24) and free or total triiodothyronine (free T3 or total T3) (17, 23, 24) and slightly decreased free thyroxine (FT4) (24). Anyway, the results are inconsistent; other studies have not found a relationship between measures of adiposity and TSH (25-27), T3 (18, 25, 26) or FT4 (17, 18, 23, 25, 27). There have been fewer researches in the field of pediatric; most of these researches have had relatively small sample sizes (21, 28-33), and also reported inconsistent results. The majority of papers found an association between TSH and BMI (15, 30-32, 34), similarly between T3 and BMI (15, 29-32, 34), but in some of the articles have not shown this association (28).

Contrary to most research in adults, there was no relationship between FT4 and BMI found in the majority of pediatric researches (15, 28-34). Considering the importance of subject and conflicting results that have been achieved in this field; so to be able to clear the indeterminacies in this regard, the presented study aimed to compare the

relative frequency of thyroid function disorders in obese and overweight children with non-obese children (as a case-control study) were conducted.

2- MATERIALS AND METHODS

2-1. Study design and population

The presented research is a case-control study, was conducted on 137 children and adolescents with overweight and obesity 6 to 18 years old (body mass index [BMI] above the 85th percentile) as the case group, and 137 non-obese children and adolescents (BMI less than 85th percentile) as the control group in Birjand city, the center of South-Khorasan province, East of Iran, during December 2015 to June 2016 (in 6 months).

2-2. Methods

Samples were selected among the student's research project metabolic syndrome students of Birjand (ID code: 610). Mentioned research project was performed on 4,340 students 6 to 18 years, contains: 1,621 students of primary school, 1,457 students of middle school and 1,262 students of high school in Birjand city the capital of South Khorasan province. Samples were selected through multiple-cluster sampling. Since, primary, middle and high schools were distributed in different districts of the city, at first girls' schools and boys' schools were selected. Following this, based on the population of each school and its ratio to the total population, primary, middle and high school students, some students were selected from each class. Samples of the case group were randomly systematically recruited among children and adolescents with overweight and obesity (including 48.18% boy and 51.82% girl, 33.57% primary, 35.77% middle and 30.66% high school) and samples of the control group among non-obese subjects, who had health records in the Atherosclerosis and Coronary Artery Research Center of Birjand city (including 48.18% boy and 51.82% girl, 33.57% primary, 35.77% middle and 30.66% high school). Based on the sample size formula and limitations in the study, 137 students with overweight and obesity as case group and 137 non-obese students as control group (in total, 274 students), were ready to cooperate and participate in the study.

2-3. Measuring

The study subjects were complete physically examined by podiatrist and pediatric resident. Weighing of the students by German Seca digital scale with 100 gram calibration weight was done, while they were barefoot and wore light clothing. The height of each student was also measured in standard manner (without shoes, in standing position, while heels sticking together and buttocks, occipital and shoulder along the straight line and the tangent with stadiometer); with an error of 0.5 cm. At the end, BMI was calculated. In order to determine overweight and obesity, the percentages of Center for Diseases Control and Prevention (CDC) were employed (35). 85-95 percentiles were taken as overweight with respect to age and gender; and $\geq$ 95 percentile was defined as obese.

2-4. Laboratory tests

Biochemical parameters include TSH, FT3 and FT4 were measured in all subjects of the case and control groups. Average and relative frequency of thyroid dysfunction in children and adolescents with obesity and overweight compared with the control group. Based on the laboratory kit, the reference range for thyroid function test (TSH), 0.4-6.2 mIU/ml, reference ranges of FT4, 0.9-1.7 ng/dl, and FT3, 3-5.07 pg/ml, were considered and values outside of this range, were regarded as abnormal thyroid function (36). Blood sample for TSH, FT3 and FT4 tests, in fasting, was taken from the cubital vein of left hand in the early morning at the Vali-e-Asr

Hospital, Birjand city. After clotting, blood serum was isolated from sample. In order to remain hormone levels stable, and prevent their destruction, after sampling, all the samples were immediately centrifuged at 25°C. Serum TSH, free thyroxine and free triiodothyronine using electro-chemiluminescence (ECL) (Roche, E411 Mannheim made in Germany) were measured.

2-5. Ethical consideration

- ✓ Obtain permission from the Ethics Committee of the Medical University and registration of study in the clinical trials system;
- ✓ Eligible children for the study, after explaining the purpose of the study to parents and informed consent were enrolled;
- ✓ No cost to the families of the studied children for experiments;
- ✓ If children have thyroid disorders, were referred to a specialist for follow-up.

2-6. Inclusion and exclusion criteria

The inclusion criteria as follows:

- Children and adolescents with overweight and obesity (BMI above the 85th percentile) inorganic non-syndromic in case group, with an age range 6 to 18 years;
- Children and adolescents in the control group (BMI less than 85th percentile), have no evidence of glandular diseases (matched in age and gender with case group);
- Obtain consent of the studied parents.

The exclusion criteria as follows:

- Children and adolescents with a history of treatment with radioactive iodine;
- Children and adolescents treated with thyroid hormone, anti-thyroid drugs or any medicines that may affect in the assessment of thyroid status;
- Children and adolescents who have glandular or metabolic disorders;
- Discontented parents to participate their child in the study.

2-7. Data Analyses

Statistical analysis was done by means of SPSS version 19.0, data checked for normality by Kolmogorov-Smirnov test. Comparing variables were performed using Chi-Square test and independent t-test. Also, according to the data normality, in order to evaluate significant relationship between BMI, TSH, FT4 and FT3 in the two groups, Pearson test were applied. $P \leq 0.05$ was taken as the significant level.

3- RESULTS

In the present study, 137 non-obese children and adolescents with mean ± standard deviation of age: 13.06 ± 2.98 year including: 66 boys (48.18%) with mean ± standard deviation (SD) of age: 12.82 ± 2.93 year and 71 girls (51.82%) with mean ± SD of age: 13.3 ± 3.03 year, as the control group (**Table.1**), and 137 children and adolescents with obesity and overweight with mean ± SD of age: 13.05 ± 3.00 year including: 66 boys (48.18%) with mean ± SD of age: 12.82 ± 3.00 year and 71 girls (51.82%) with mean ± SD of age: 13.27 ± 3.01 year, as the case group (**Table.2**), were studied.

In **Tables.1 and 2**, mean ± SD of BMI in children and adolescents on the basis of gender is also shown. In this study, the mean ± SD TSH, FT4 and FT3 of children and adolescents in the control group, were: 1.97 ± 0.63 mIU/ml, 1.45 ± 0.13 ng/dl and 4.09 ± 0.39 pg/ml, respectively, and in the case group, were: 4.32 ± 1.01 mIU/ml, 1.28 ± 0.18 ng/dl and 3.92 ± 0.53 pg/ml, respectively. The results reveal that children and adolescents with obesity and overweight had TSH more than non-obese subjects ($P<0.001$), while they had FT4

(P<0.001) and FT3 (P=0.003), less than non-obese children and adolescents.

In **Table.3**, mean comparison of the control and case groups data based on the independent t-test, is reported. As seen in the table, the mean difference for all parameters is statistically significant. Determine and compare the relative frequency of thyroid dysfunction in the two groups (case and control) showed that in the control group, a 11-year-old boy (0.73%), and in the case group, 4 subjects (2.92%), include three girls and one boy with mean ± SD of age: 11.5 ± 2.08 year, have hypothyroid disorder. The mean comparison of subjects with hypothyroidism disorder (using independent t-test) between the two groups was not significant (P= 0.177).

Indeed, the frequency of thyroid disorder in children and adolescents of the case group was more than the control group, but the difference was not statistically significant. Also, the average TSH of children and adolescents with hypothyroid disorder in the case group (8.52± 0.585 mIU/ml) was more than the control group (7.50 ± 0.413 mIU/ml), while average FT4 and FT3 in the case group (0.65 ± 0.042 ng/dl and 2.78 ± 0.086 pg/ml, respectively) less than average FT4 and FT3 in the control group (0.70± 0.023 ng/dl and 2.80+ 0.017 pg/ml, respectively).

In **Table.4**, the relationship between BMI, TSH, FT4 and FT3 in non-obese children and adolescents (control group) were examined using Pearson test. As can be seen, there isn't significant relationship between BMI with TSH (P= 0.185), FT4 (P= 0.140) and FT3 (P= 0.161); but there is a significant relationship between TSH with FT4 (P <0.001) and FT3 (P <0.001). In this group, relationship between FT4 and FT3 was not significant (P = 0.060).

Also in **Table.5**, the relationship between BMI, TSH, FT4 and FT3 in children and adolescents with overweight and obesity (case group), were reported (based on Pearson test). According to the results, there was not significant relationship between BMI with TSH (P = 0.920), FT4 (P = 0.248) and FT3 (P = 0.304); while there was a significant relationship between TSH with FT4 (P <0.001) and FT3 (P= 0.001). There was also highly significant relationship between FT4 and FT3 (P <0.001).

Table-1: Statistical information (number, age, sex and BMI) of non-obese children and adolescents

Samples	Number (%)	Mean ± SD of age (year)	Mean ± SD of BMI (Kg/m^2)
Boys	66(48.18)	12.82 ± 2.93	18.73 ± 1.94
Girls	71(51.82)	13.3 ± 3.03	18.96 ± 1.95
Total	137(100)	13.06 ± 2.98	18.85 ± 1.94

BMI: Body mass index; SD: Standard deviation.

Table-2: Statistical information (number, age, sex and BMI) of children and adolescents with obesity and overweight

Samples	Number (%)	Mean ± SD of age (year)	Mean ± SD of BMI (Kg/m^2)
Boys	66(48.18)	12.82 ± 3.00	24.38 ± 2.88
Girls	71(51.82)	13.27 ± 3.01	24.72 ± 2.84
Total	137(100)	13.05 ± 3.00	24.56 ± 2.86

BMI: Body mass index; SD: Standard deviation.

Table-3: Mean comparison and standard deviation of BMI, TSH, FT4 and FT3 in the case and control groups

Variables	Group	Mean	Standard deviation	P-value (t-test)
BMI (Kg/m^2)	Control	18.8526	1.94536	<0.001
	Case	24.5591	2.85556	
TSH (mIU/ml)	Control	1.9694	0.63198	<0.001
	Case	4.3200	1.01063	
FT4 (ng/dl)	Control	1.4526	0.13196	<0.001
	Case	1.2832	0.17902	
FT3 (pg/ml)	Control	4.0890	0.38835	0.003
	Case	3.9183	0.53460	

BMI: Body mass index, TSH: Thyroid stimulating hormone, FT3: Free triiodothyronine, FT4: Free thyroxine.

Table-4: Significant relationship between BMI, TSH, FT4 and FT3 in the control group, using Pearson test

Variables	BMI (Kg/m^2)	TSH (mIU/ml)	FT4 (ng/dl)	FT3 (pg/ml)
BMI* (Kg/m^2)	-	0.185	0.140	0.161
TSH* (mIU/ml)	0.185	-	<0.001	<0.001
FT4* (ng/dl)	0.140	<0.001	-	0.060
FT3* (pg/ml)	0.161	<0.001	0.060	-

BMI*: Body mass index, TSH: Thyroid stimulating hormone, FT3: Free triiodothyronine, FT4: Free thyroxine

Table-5: Significant relationship between BMI, TSH, FT4 and FT3 in the case group, using Pearson test

Variables	BMI (Kg/m^2)	TSH (mIU/ml)	FT4 (ng/dl)	FT3 (pg/ml)
BMI (Kg/m^2)	-	0.920	0.248	0.304
TSH (mIU/ml)	0.920	-	<0.001	0.001
FT4 (ng/dl)	0.248	<0.001	-	<0.001
FT3 (pg/ml)	0.304	0.001	<0.001	-

BMI: Body mass index, TSH: Thyroid stimulating hormone, FT3: Free triiodothyronine, FT4: Free thyroxine.

4- DISCUSSION

Based on the results of this study, children and adolescents with obesity and overweight had TSH more than normal subjects, while they had FT4 and FT3 less than normal children and adolescents. This relationship could offer an association with leptin, which is regulated by body adiposity (37). Moreover, there is a synchronicity between the secretion of leptin and TSH (38). A recent report demonstrated that TSH is related both to BMI and to leptin in obese and anorexic patients (32). Nevertheless a previous research had revealed no correlation between TSH and leptin (39). Also, as regards TSH production is regulated by several transmitters and hormones which regulates also body weight and satiation, such as neuropeptide Y, alpha-melanocyte-stimulating hormone and leptin itself (40-41), a mechanism of regulation of TSH more complicated than a simple linear relation between TSH and leptin levels. In the other words a tissue-specific modulation of deiodinases at pituitary level might be implicated in the effect of leptin on thyroid function. Researches in animal models indicate that leptin administration can reduce type

II deiodinase (D2) activity in pituitary tissue, thus modifying the feedback of T3 on TSH secretion (42). At least some of the thyroid abnormalities observed in severe obesity are reversible with weight loss (43), offering the possibility of dysregulated signaling by obesity-related humoral factors. Potential reasons of the observed thyroid dysregulation seen in obesity include adiposity-induced thyrotropin-releasing hormone over-secretion, TSH resistance or adaptations that increase energy expenditure (16, 44). Adipose tissue-derived leptin regulates energy balance in part through the hypothalamic-pituitary-thyroid axis using upregulating hypothalamic thyrotropin-releasing hormone gene expression (16), and can also stimulate conversion of T4 to T3 via activation of thyroid deiodinases (16). Prior study supports the close relationship between thyroid hormones and leptin, in a positive relationship has been found between TSH and leptin in longitudinal and cross-sectional analyses (32). Leptin has also been realize to be inversely correlated with FT4 (25).

Maybe the greater amounts of fat mass found among obese adolescents exert greater physiological effects that are easier to observe. It is possible that subclinical autoimmune thyroiditis is more prevalent in adolescents and intensified. Perhaps to follow this thyroiditis, FT3 as well as FT4, is reduced. However, the reversibility of thyroid abnormalities with weight loss that has previously been described in adolescents (44) is not consistent with this explanation. The results of present study are compatible with many similar studies, that here we mention some of them: study of Ghergherehchi and Hazhir that was done during 2011 to 2013 on 190 children with obesity and overweight, and 133 normal children in Tabriz, revealed total levels TSH and T4 in obese and overweight children compared with the control group was significantly higher. There was a significant positive relationship between BMI and levels of TSH and T4. In this study was also measured thyroid antibodies, and cause of autoimmune rejected, and was mentioned that increase of total levels TSH and T4 associated with obesity, is without interfering antibody and can be reduced with decrease of BMI (21). Study of Grandone et al., also showed that increase the average of TSH concentration, often seen in obese children (15). As well as, the research results of Matusik et al., revealed the relationship between high BMI and high TSH (45). The results of Torun et al., determined that serum concentration of TSH and FT3 in obese children was higher than the control group, but in FT4 was not significantly different between the two groups (obese and normal) (46).

The results of other study of Torun et al., showed that in obese children, TSH levels were significantly increased as the degree of hepatic steatosis, but levels of FT3 and FT4 not significantly different (47). The results of Reinehr and Andler also revealed that TSH, T3 and T4 were significantly higher in obese children compared with normal weight subjects. Also, 12%, 15% and 11% of obese children had respectively TSH, T3 and T4 levels higher than double the standard deviation of normal weight children and the degree of overweight was in related with T3, T4 and TSH (34). In study of Grandone et al., in 2010, among 938 children and adolescents with obesity was done, BMI and FT3 level in patients with increased TSH was higher than those who had normal TSH (15).

According to the present study in the control group, one child (n= 0.73%), and in case group, four children (2.92%) had hypothyroidism disorder, but this difference was not statistically significant. In study of Ghergherehchi and Hazhir, subclinical hypothyroidism in obese children (14.7%), compared with normal children (8.6%), was significantly higher

(21). In study of Grandone et al., Hyper-thyrotropinemia (TSH ≥ 4.2 μUI/ml) were reported in 12.8% obese children and adolescents (15). In our study, the prevalence of subclinical hypothyroidism is less than two studies of Ghergherehchi and Hazhir, and Grandone et al. that could be due to differences in the defined normal range in these studies with the present study. Pearson test revealed that in non-obese children and adolescents (control group), there was not significant relationship between BMI with TSH, FT4 and FT3; but there was a significant relationship between TSH with FT4 and FT3. In this group, relationship between FT4 and FT3 was not significant. Pearson's test also showed that in children and adolescents with overweight and obesity (case group), there was not significant relationship between BMI with TSH, FT4 and FT3; while there was a significant relationship between TSH with FT4 and FT3. There was also highly significant relationship between FT4 and FT3.

A study carried out in 2015 by Krause et al., in order to examine associations of weight and adiposity with indices of thyroid function and thyroid-related metabolic factors in children. Based on their results, TSH was positively related to BMI-Z score (BMIz) and fat mass (both P-values<0.001). FT4 was negatively related to BMIz and fat mass (both P-values<0.001). TSH was positively correlated to leptin (P= 0.001) even after accounting for fat mass. They expressed: pediatric obesity is associated with higher TSH and lower FT4 concentrations and with a greater prevalence of abnormally high TSH. Leptin concentrations may in part explain obesity's effects on thyroid status, perhaps through leptin's effects on TSH secretion (48). In a review study during 2012 by Pacifico et al., thyroid function in relation to obesity of childhood, were investigated. They expressed elevated TSH concentrations in association with normal or slightly elevated free T4 and/or free T3 levels have been consistently found in obese subjects, but the mechanisms underlying these thyroid hormonal changes are still unclear. Whether higher TSH in childhood obesity is adaptive, increasing metabolic rate in an attempt to reduce further weight gain, or indicates subclinical hypothyroidism or resistance and thereby contributes to lipid and/or glucose dysmetabolism, remains controversial. According to the results of this review study, lifestyle intervention have a potential role in the treatment of thyroid disorders in obese children (49). In some researches subclinical hypothyroidism has been revealed to worsen metabolic profile, causing dyslipidemia or heart dysfunction (50). According to the relationships between thyroid dysfunction and obesity; lifestyle modification, including: proper nutrition and encouraging physical activity, to reduce weight and improve thyroid function tests in children and adolescents with obesity and overweight and perform interventional studies in this area is recommended.

5- CONCLUSION

Based on the results of present study, overweight and obesity is associated with increasing TSH and hypothyroidism, and decreasing FT4 and FT3. According to the contradictory results in different studies about the relationships between thyroid hormone levels and obesity, long-term studies with larger sample size is suggested.

6- CONFLICT OF INTEREST

The authors had not any financial or personal relationships with other people or organizations during the study. So there was no conflict of interests in this article.

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