

Thyroid Function Status in Obese Children

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Abstract

Introduction: The prevalence of obesity in all age groups has increased dramatically over the past 30 years, such that overweight and obesity are considered to be a major public health concern in many countries. Obesity affects hypothalamic-pituitary-thyroid axis directly or indirectly leading to alterations in thyroid function tests.

Aim of the study: To evaluate thyroid function in obese children and to correlate it with different parameters.

Subjects and methods: This study included two groups; *Group I*: 40 obese patients where obesity was defined according to the body mass index (BMI) above the 95th percentile for age and sex using the definition of the International Task Force for obesity in Childhood and *Group II*: 40 children age and sex matched as a control group. They were subjected to: Thorough history taking, clinical examination, anthropometric measurements and laboratory investigations including; fasting blood sugar, total cholesterol and triglycerides, thyroid Function Tests (TSH, free T3, free T4 and anti- thyroglobulin anti-bodies (Tg-Ab).

Results: 35% and 40% of obese children had increased serum levels of TSH and free T3 respectively. Also, there were significant differences between cases and controls as regard: TSH, free T3 and insignificant difference as regard free T4. None of our patients had *anti TG titre* positivity. There were significant correlations between TSH with BMI, triglycerides and cholesterol while there was insignificant correlation between FT3 with BMI.

Conclusion: Some obese children show thyroid function tests abnormality in the form of increased TSH and FT3. Furtherly, none of them show anti TG positivity values. So, thyroid autoimmunity does not play a significant role in thyroid changes noted in obese children.

Keywords: Obesity; Thyroid function; Autoimmunity; Children; Cholesterol; anti TG

Introduction

Obesity is considered a worldwide health problem and its prevalence is increasing steadily and dramatically all over the world [1]. Pediatricians are often involved in the initial evaluation of pediatric obesity and its numerous co-morbidities. Obese individuals are, in fact, at high risk of developing dyslipidemia, hypertension and impaired glucose tolerance, with the consequent increase of their risk of metabolic and cardiovascular diseases [2]. There had been an increasing attention to thyroid function in pediatric obese patients [3]. Hypothyroidism has often been thought to be the cause of obesity, and thyroid function tests are still now one of the most commonly performed laboratory analysis in this population. Isolated hyperthyrotropinemia is a condition characterized by a serum TSH above the statistically defined upper limit of the reference range with normal or slightly high serum free T4 (fT4) and free T3 (fT3) concentration [4].

Whether or not increased TSH levels affect the metabolic and cardiovascular profile in obese children and adolescents remains unclear, as well as TSH decrease after weight loss. Thereby, there still is considerable disagreement regarding treatment [5].

Aim of the Study

To evaluate thyroid function in obese children and to correlate it with different parameters.

Subjects and Methods

This study was a cross-sectional study which included two groups.

Group I, 40 children diagnosed with obesity according to their body mass index (BMI) which exceeding 95th percentile suitable for age and sex according to Egyptian Growth Charts (2002). This

definition of obesity was based on the International Task Force for Obesity in Children [6]. They were randomly selected from pediatric endocrinology outpatient's clinic, Minia university children hospital. They were collected from June 2011 to December 2011. They were 30 males (75%) and 10 females (25%) with an age ranged from 2 years-16 years old with a mean of 8.04 ± 4.4 .

Group II included 40 apparently healthy children age and sex matched with the patient group. An informed consent was obtained by care giver of every child.

In exclusion criteria, obese patients with any obesity complications, presence of goiter or known thyroid disease, any medications altering blood pressure, glucose or lipid metabolism, patients with medical syndromes associated with obesity and patients with family history of thyroid diseases. The studied groups were subjected to; thorough history taking, clinical examination, anthropometric measurements (weight, height, BMI, with plotting on the Egyptian growth charts suitable for age and sex to obtain a percentile ranking, waist circumference), laboratory investigations including: fasting blood sugar (Assayed by using fully automated clinical chemistry auto-analyzer system Konelab 20i (Thermo Electron Incorporation, Finland), total cholesterol and TG by using fully automated clinical chemistry

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auto-analyzer system Konelab 20i (Thermo Electron Incorporation, Finland). Thyroid Function Tests (TSH by solid phase sandwich ELISA method with a normal range 0.7-6.4 uIU/ml) [7], free Triiodothyronine (fT3) which was measured by radioimmune assay using commercial kits (normal range 1.4-4.2 pg/ml) [8], free Thyroxine (fT4) which was measured by radioimmune assay using commercial kits (normal range 0.8-2.0 ng/ml) [9] and anti-thyroglobulin anti-bodies (Tg-Ab): with references (normal: <100 IU/ml, borderline: 100-150 IU/ml and elevated: >150 IU/ml) [10].

Statistical Methodology

Standard computer program SPSS for windows, release 15.0 (SPSS Inc, USA) was used for data entry and analysis [11]. All numeric variables were expressed as mean ± standard deviation (SD). Comparison of different variables in various groups were done using student t-test and Mann Whitney test for parametric and non-parametric variables respectively. Chi square test (X²) was used to compare frequency of qualitative variables among the different groups. Pearson's and Spearman's correlation tests were used for correlating parametric and non-parametric variables respectively. Multiple regression analysis was also performed to determine effect of various factors on a dependent variable. P-value < 0.05 was significant.

Results

Figure 1 showed that 14 children (35.35%) of the obese group had hyper-thyrotropinemia (TSH ≥ 6.4 micr IU/ml). Moreover, the obese group had significant higher levels of TSH, fT3, triglycerides and cholesterol than the control group, while there were insignificant differences between them as regard fT4, anti-TG (Table 1).

Table 2 showed that obese group with hyper-thyrotropinemia had significant higher levels of fT3, triglycerides, cholesterol and FBS than those without hyper-thyrotropinemia. On the other hand, there were insignificant differences between them as regard fT4 and anti-TG.

Regarding different associations, (Table 3 and Figures 2-4) showed that TSH had significant positive correlations with BMI, fT3, triglycerides, cholesterol and FBS, while there was a significant negative correlation between TSH and fT4. Moreover, there were significant positive correlations between fT3 and age, triglycerides, cholesterol and FBS (Table 4 and Figure 5). Finally, there was a significant positive correlation between fT3 and fT4 (Figure 5).

Discussion

Childhood obesity is associated with substantial comorbidity and late sequelae including; Type 2 Diabetes, hypertension, liver disease and cardiovascular complications [12,13].

The relationship between obesity and thyroid dysfunction is a

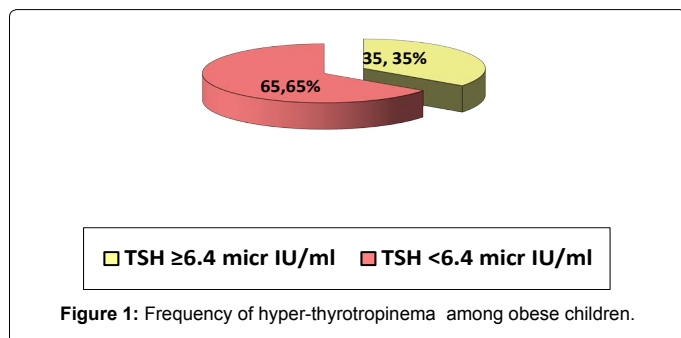


Figure 1: Frequency of hyper-thyrotropinemia among obese children.

Variable		Obese group (N=40)	Control group (N=40)	P-value
TSH (µIU/ml)	Range	0.80-7.5	0.90-4	0.0001*
	Mean ± SD	3.5 ± 2.4	1.7 ± 0.85	
fT3 (pg/ml)	Range	1.1-5.5	1.1-4	0.0001*
	Mean ± SD	3.7 ± 1.1	2.3 ± 0.92	
fT4 (ng/ml)	Range	0.80-1.70	1-1.6	0.11
	Mean ± SD	1.38 ± 0.21	1.32 ± 0.16	
Anti-TG(IU/ml)	Range	13-130	30-100	0.72
	Mean ± SD	64.4 ± 33.1	66.8 ± 26	
Triglycerides (mg/dl)	Range	100-235	85-120	0.0001*
	Mean ± SD	141.7 ± 25.8	101.9 ± 11.5	
Cholesterol (mg/dl)	Range	110-239	90-150	0.0001*
	Mean ± SD	180.3 ± 34.4	123 ± 16.2	
FBS (mg/dl)	Range	74-120	73-115	0.46
	Mean ± SD	94.6 ± 12.5	92.8 ± 12.3	

TSH = Thyroid-stimulating hormone; fT3 = Free Triiodothyronine; fT4 = Free Thyroxine; TG = Thyroglobulin; * = significant.

Table 1: Comparison between obese and control groups as regard hormonal and biochemical variables.

Variable		TSH ≥ 6.4 micrIU/ml (N=14)	TSH < 6.4 micrIU/ml (N=26)	P-value
fT3 (pg/ml)	Mean ± SD	4.68 ± 0.23	3.26 ± 1.17	0.0001*
fT4 (ng/ml)	Mean ± SD	1.3 ± 0.23	1.4 ± 0.18	0.052
Anti-TG(IU/ml)	Mean ± SD	70.9 ± 32.7	61 ± 33.4	0.37
Triglycerides (mg/dl)	Mean ± SD	164.2 ± 26.3	129.5 ± 15.5	0.0001*
Cholesterol (mg/dl)	Mean ± SD	203.2 ± 26	168 ± 32.4	0.001*
FBS (mg/dl)	Mean ± SD	109 ± 9.4	84.1 ± 10.7	0.002*

TSH = Thyroid-stimulating hormone; fT3 = Free Triiodothyronine; fT4 = Free Thyroxine; TG = Thyroglobulin; * = significant.

Table 2: Comparison between the obese group with and without hyperthyrotropinemia as regard hormonal and biochemical variables.

Variable	r	P
Age(year)	0.250	0.120
BMI(k/m ²)	0.527	0.0001*
fT3(pg/ml)	0.612	0.0001*
fT4(ng/ml)	-0.317	0.046*
Triglycerides(mg/dl)	0.628	0.0001*
Cholesterol(mg/dl)	0.520	0.001*
FBS(mg/dl)	0.511	0.001*

* = significant.

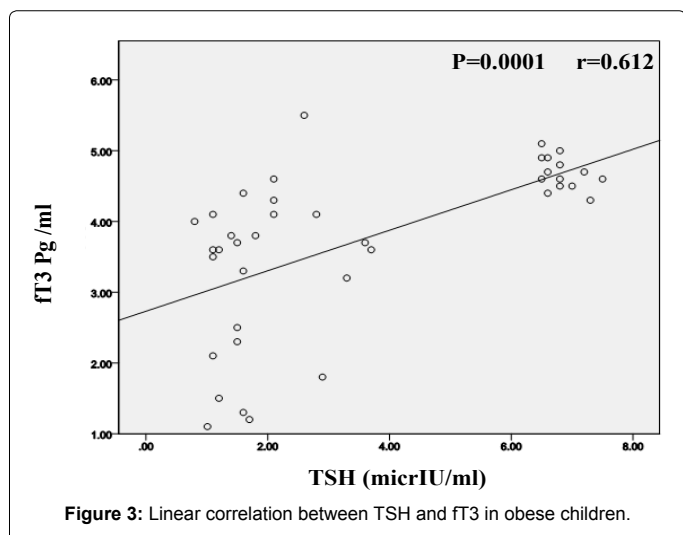
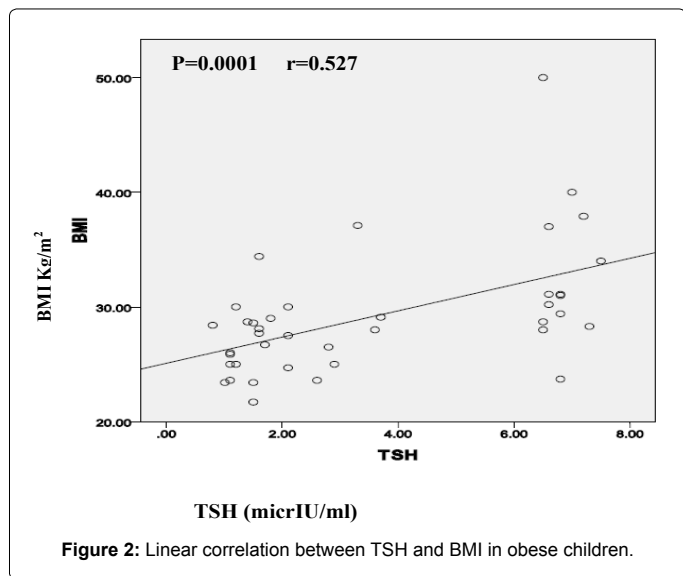
Grades of r: 0.00 to 0.24 (weak or no association), 0.25 to 0.49 (fair association), 0.50 to 0.74 (moderate association) and ≥0.75 (strong association).

Table 3: Correlations between TSH with clinical and laboratory parameters.

topic of great interest, as a large number of obese children now seeking medical care [14]. Taking into consideration that obesity affects pituitary thyroid axis resulting in thyroid function changes. Thyroid hormones and TSH concentrations in obesity had been studied and were variously described as normal, elevated, or even low in obese subjects compared with normal weight controls.

We evaluated thyroid function tests in 40 obese children: 30 males (75%), 10 females (25%) with an age ranged from 2 - 16 years old and another 40 non obese age and sex matched children as a control group.

As regard the results of the current study, (35.35%) of the obese group had hyper-thyrotropinemia (defined in our study as TSH > 6.4 IU/ml) versus none of the control group and described as (Isolated hyperthyrotropinemia) (Figure 1). This result was in agreement with the results obtained by: Stichel et al. [3], Eliakim et al. [15], Reinehr



et al. [16], Bhowmick et al. [17], Shalitin et al. [5] and Grandone et al. [14].

This finding could be explained by several mechanisms which lead to hyper-thyrotropinemia and had been hypothesized, including increased leptin-mediated production of pro-TRH, impaired feedback due to a lowered number of T3 receptors in the hypo-thalamus, and variations in peripheral deiodinase activity.

Nevertheless, abnormalities in thyroid function and TSH mostly normalize after weight loss, independent of whether the loss is obtained with diet or bariatric surgery, suggesting that these biochemical alterations are reversible [18].

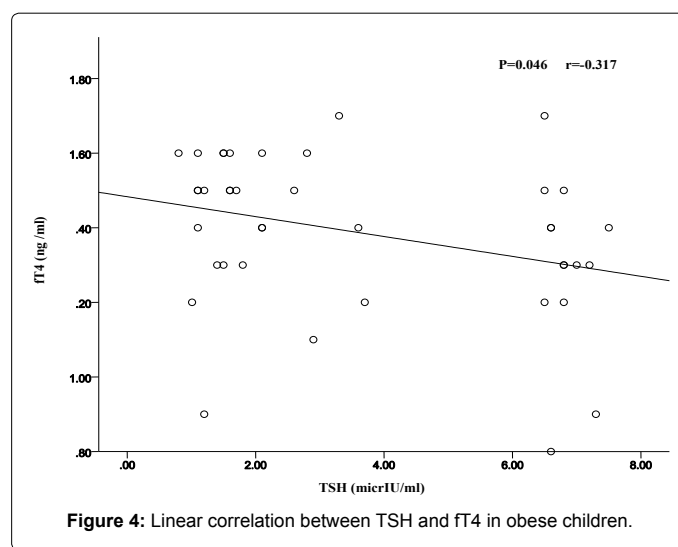
There was another explanation where higher TSH in childhood obesity is adaptive, increasing metabolic rate in an attempt to reduce further weight gain, or indicates subclinical hypothyroidism or resistance and thereby contributes to lipid and/or glucose dys-metabolism.

Concerning thyroid antibodies, none of our studied cases (0%) showed anti TG titre positivity. This finding confirmed that the increase in TSH was not accounted by autoimmune thyroiditis [3].

This result was in contrast with the results of Stichel et al. [3] where they found positive thyroid auto-antibodies in 5.7%; Eliakim et al. [15] found 19.5% and Radetti et al. [18] found 23% of their obese children had positive thyroid autoantibodies.

Concerning hormonal biochemical variables, this study found that the obese group had significant higher levels of TSH and fT3 than the control group where (P=0.0001) for each (Table 1). On the other hand, there was insignificant difference between them as regard fT4, this result was in agreement with Stichel et al. [3] and Reinehr et al. [16] who reported insignificant difference between cases and controls as regards T4 and fT4 respectively.

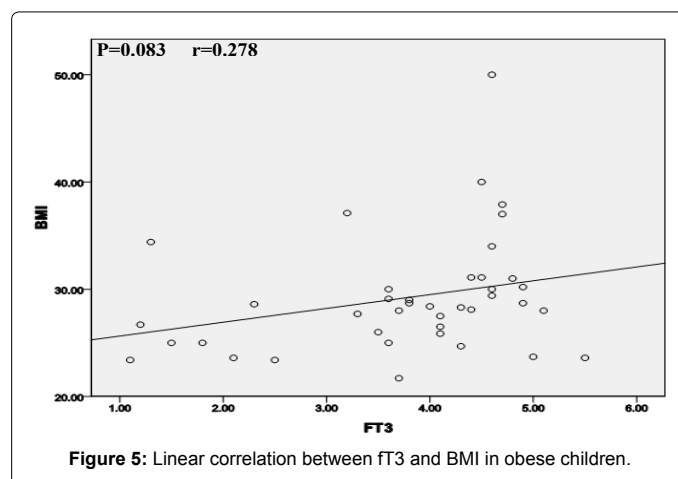
Moreover, obese group had significant higher levels of triglycerides



Variable	r	P
Age(year)	0.367	0.020*
BMI(Kg/m)	0.278	0.083
fT4(ng/ml)	0.083	0.609
Triglycerides(mg/dl)	0.582	0.0001*
Cholesterol(mg/dl)	0.460	0.003*
FBS(mg/dl)	0.437	0.005*

* = significant.

Table 4: Correlations between fT3 with clinical and laboratory parameters.



and cholesterol than the control group where ($P=0.0001$) for each (Table 1). This could be explained by that obesity has a negative effect on lipid levels in the blood, which often lead to the development of a condition known as dyslipidemia. This abnormal shift in lipid levels is due to weight gain. So, losing weight conversely has an opposite effect [19].

As regard hormonal and biochemical variables in obese group with and without hyper-thyrotropinemia, the current study found that those with hyper-thyrotropinemia had significant higher levels of fT_3 , triglycerides, cholesterol and FBS where ($P=0.0001, 0.0001, 0.001$ and 0.002) respectively (Table 2). This could be explained by the increase of TSH levels is associated with increased fT_3 due to changes in the mono-deiodination pathway [16,20]. Approximately 80% of circulating T_3 is derived by extra-thyroidal mono-deiodination of T_4 , whereas reverse T_3 (rT_3) is almost completely produced by extra-thyroidal T_4 mono-deiodination [21].

In normal weight humans, mono-deiodination of T_4 produces approximately equal amounts of T_3 and rT_3 . However, in obesity, production of rT_3 is decreased while production of T_3 is increased [22]. Increased thyroid hormone could point to hormone resistance, similar to insulin resistance in obesity [23].

In support of this theory, the fact that in obesity the number of T_3 receptors are decreased and the negative feedback between TSH and the peripheral thyroid hormones is decreased, where both TSH and the peripheral thyroid hormones are increased in obesity [16,20,23,24], so to determine whether pituitary responsiveness is altered in obese children a TRH test could be useful.

Concerning different correlations, the current study found that TSH had significant positive correlation with BMI where ($r=0.527$) and ($P=0.0001$) (Table 3) and (Figure 2). This result was in agreement with Grandone et al. [14] and Marras et al. [19]. On the other hand, it was in contrast to Hari Kumar et al. [25] and Aeberli et al. [26].

This correlation could suggest an association with leptin, which is regulated by body adiposity [27]. Furthermore, there is a synchronicity between the secretion of leptin and TSH. There was a report demonstrated that TSH is related both to BMI and to leptin in obese and anorexic patients [20]. Furthermore, considering that 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. A mechanism of regulation of TSH more complicated than a simple linear association among TSH and leptin levels, could be inferred to explain this lack of association [28]. For example a tissue-specific modulation of deiodinases at pituitary level might be implicated in the effect of leptin on thyroid function. Studies in animal models show that leptin administration can decrease D2 deiodinase activity in pituitary tissue, thus modifying the feedback of T_3 on TSH secretion [29]. Moreover, TSH had a significant positive correlation with fT_3 ($r=0.612$ and $P=0.0001$). On the other hand, it had a significant negative correlation with fT_4 where ($r=-0.317$ and $P=0.046$) (Figures 3 and 4).

As regard correlation between fT_3 and different parameters, the current study found that it had significant positive correlations with age, TG, cholesterol and FBS (Table 4).

On the other hand, there was insignificant correlation between it and BMI (Figure 5). This was in contrast to the results obtained by Grandone et al. [14] and Marras et al. [25] who reported a significant positive correlation between fT_3 and BMI.

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