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Childhood obesity, thyroid function, and insulin resistance – is there a link? A longitudinal study

Abstract

Background: Serum thyroid stimulating hormone (TSH) levels are frequently elevated in obese children and are most likely to be associated with insulin resistance. However, clinical relevance of this association remains unclear.

Objectives: To assess the prevalence of hyperthyrotropinemia; to analyze the relationship between TSH and homeostasis model assessment – insulin resistance (HOMA-IR); and to verify whether TSH levels and HOMA-IR vary with weight loss in obese children.

Subjects and Methods: Retrospective longitudinal study with data from baseline and 1 year after lifestyle intervention in a pediatric obese group (344 children were recruited and 100 among them completed follow-up). For postintervention analysis, three groups were considered according to body mass index-standard deviation score (BMI-SDS) variations: ≤ -0.5 (significant weight loss); $0.5-0$ (weight loss); and >0 (weight gain). Statistical analysis was performed using SPSS 19.0®.

Results: The prevalence of increased TSH levels was 9.3%. At baseline TSH ($p=0.007$), fT4 ($p=0.006$), and HOMA-IR ($p<0.001$) were positively correlated to BMI-SDS ($n=344$). Weight reduction was verified in 67 out of 100 cases but significant loss was present in only 21 cases. Decreases in both TSH and BMI-SDS were independently associated with decreases in HOMA-IR ($p=0.005$ and $p=0.016$, respectively). There was no correlation between TSH and BMI-SDS variation. Significant decreases in the HOMA-IR ($p=0.006$) were only achieved in the significant weight loss group.

Conclusions: The prevalence of hyperthyrotropinemia was lower than previously reported. However, cutoff values were adjusted to pubertal stage, suggesting an over report in other studies. Insulin resistance and TSH were positively correlated, independent of body status. Although weight loss was not associated with TSH variation, a decrease in TSH levels was independently associated with decreases in HOMA-IR.

Keywords: insulin resistance; obesity; pediatric; thyroid hormones; weight loss.

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Introduction

The growing prevalence of overweight and obesity is becoming an increasingly important health problem throughout the world, as obese children have greater likelihood than normal weight children to develop dyslipidemia, high blood pressure, and impaired glucose metabolism, which significantly increase their risk for cardiovascular and metabolic diseases (1–9).

Several endocrine abnormalities are reported due to obesity (9, 10). Some of these abnormalities are considered to be secondary effects of obesity and are usually restored after weight loss (10). Several studies report a positive correlation between serum levels of thyroid stimulating hormone (TSH) and body mass index (BMI) (1, 3–6, 9, 11–14). These data suggest that thyroid function, even within the normal range, can be one of the several factors contributing to determining body weight. Obese children may have moderately elevated TSH levels in association with normal or slightly elevated free thyroxine (fT4) and/or free triiodothyronine (fT3) levels, suggesting an adaptation process for increasing energy expenditure (1). Increased TSH levels, in obese children, have been reported to normalize after substantial weight loss, but no overall consensus has been reached (1, 3, 9, 14–17).

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The metabolic changes and increased cardiovascular risk described in the metabolic syndrome are very similar to the changes seen in hypothyroidism (1, 18). Some studies report that obese children with high TSH levels have more severe insulin resistance than obese children with normal TSH levels, with HOMA-IR positively correlating with TSH levels (5, 16). Some authors attribute this relationship to weight variation and not to thyroid function (1, 14).

There is still a considerable disagreement regarding thyroid dysfunction and other metabolic disorders in obese children, and whether these changes are reversible after weight reduction. In order to achieve a better understanding of this problem, we aimed: 1) to determine the prevalence of hyperthyrotropinemia in obese children and adolescents; 2) to verify whether TSH levels in childhood obesity are related to insulin resistance; and 3) to verify whether TSH levels and insulin resistance decrease with weight loss.

Materials and methods

A retrospective longitudinal study was conducted. Subjects were obese children and adolescents (2.4–19.8 years old) referred to the outpatient clinic at a tertiary hospital from 2008 to 2012 (5 years).

Subjects were excluded if they had endogenous obesity, hypothyroidism, autoimmune thyroiditis, thyroid medication or steroids, diabetes or other endocrine disease, cancer, acute or chronic inflammatory diseases, or presence of any syndrome or disease known to affect body composition or fat distribution.

All anthropometric and biochemical measures were determined at baseline and at the end of the 1 year lifestyle modification program.

Anthropometric measures

Body weight was measured using an electronic digital balance (model 910; Seca, Reinach, Switzerland) to the nearest 0.1 kg, in standing position, in light clothing without shoes, with weight evenly distributed on both feet, according to the World Health Organization criteria (19). Height was measured to the nearest 0.1 cm with a stadiometer (model 222; Seca), with the subject assuming the anthropometric position, placing the heels, buttocks, and back against the scale (20). The BMI was calculated as weight in kilograms divided by height in meters squared and obesity was defined as BMI over the 95th percentile for age and sex. To compare BMI values across different ages and by gender, we used BMI-standard deviation score (BMI-SDS) percentiles calculated according to the Center for Disease Control and Prevention growth charts (21). Pubertal stage was assessed according to Tanner's criteria.

Biochemical assays

Blood samples were obtained after a 10-h overnight fast for the determination of glycemia, insulinemia, TSH, fT4, and fT3.

Insulin resistance was estimated by HOMA-IR=[fasting insulin ($\mu\text{U/mL}$) \times fasting glucose (mmol/L)/22.5]. Increased insulin resistance was present if HOMA-IR levels exceeded 2.5 (22).

Serum insulin was measured by chemiluminescent immunoassay (DXI Unicel 800, Beckman Coulter, Brea, CA, USA) and serum TSH, fT4, and fT3 levels were measured by chemiluminescent immunoassay (DXI Unicel 600, Beckman Coulter). The reference ranges for TSH were 0.55–6.2 and 0.52–3.7 $\mu\text{U/L}$, for fT4 were 0.8–1.72 and 0.6–1.47 ng/dL, and for fT3 were 1.4–5.14 and 1.3–4.9 pg/dL, for children and pubertal individuals, respectively.

Lifestyle modification program

All subjects underwent a lifestyle modification program. Dietary guidelines were proposed to both subjects and parents, taking into account subject's age and family dietary patterns; the adoption of a normocaloric Mediterranean diet, based on a balanced distribution of carbohydrates (55%), proteins (15%), and lipids (30% total, with <10% saturated fat) was prescribed. Aerobic exercise 3–5 times per week for at least 45–60 min was also recommended. Children were advised to reduce sedentary behavior (particularly television and video games) to <2 h per day.

The study protocol was approved by the Hospital's Ethics Committee.

Statistical analysis

All values are presented as mean \pm standard deviation or frequency distribution as appropriate. Dropout and nondropout subjects were compared at baseline. Continuous variables were compared with independent samples' t test with Welch correction if equal variances could not be assumed. Categorical variables were compared with χ^2 test and significant differences were further analyzed with adjusted residuals. Bivariate Pearson correlations were calculated to analyze associations between thyroid function, BMI-SDS, and HOMA-IR at baseline. Multiple linear regression models were used to test associations at baseline, controlling for age, gender, and pubertal state.

Taking into account previous studies where improvements in the metabolic profile only occurred in the presence of significant weight loss (i.e., a decrease >0.5 in BMI-SDS) (4, 5, 23), the sample was divided into three groups according to the degree of weight loss: increase in BMI-SDS; decrease in BMI-SDS between 0 and 0.5; and decrease in BMI-SDS >0.5.

Prepost intervention values were recorded and absolute differences (Δ) were used to measure intervention effects. Prepost mean differences between BMI-SDS groups were analyzed with the Kruskal-Wallis test due to nonGaussian distribution. Posthoc analysis was conducted to examine significant differences between groups in which Kruskal-Wallis test was significant, with p-value adjustment for multiple comparisons. A p value ≤ 0.05 was considered significant. Data were analyzed with IBM SPSS 19.0[®] software (Armonk, NY, USA).

Results

Three hundred and forty-four patients were enrolled and 100 (29.1%) among them completed the 1 year lifestyle

Table 1 Baseline characteristics according to pubertal stage.

	Prepubertal	Pubertal
n	127	217
Male, %	54.3	47.5
Age, years	8.8±2.2	13.4±2.2
BMI-SDS	3.0±0.7	2.9±0.6
TSH, mU/L	2.7±1.1	2.4±1.2
ft3, ng/dL	4.5±0.6	3.9±0.4
ft4, pg/mL	1.2±0.3	1.1±0.4
HOMA-IR	2.9±1.8	3.9±2.3

modification program. Clinical characteristics of the patients initially enrolled in the study are shown in Table 1. The causes of dropout included: loss of follow-up; absence of biochemical re-evaluation after the 1 year intervention; and development of exclusion criterion during follow-up.

No significant differences were found between dropout and nondropout subjects at baseline.

Association between variables at baseline

Baseline TSH and HOMA-IR levels were increased in 32 (9.3%) and 239 (69.5%) subjects, respectively, with no significant difference by sex. Pubertal subjects had a significantly higher prevalence of hyperthyrotropinemia (13.8% vs. 1.6%, respectively, $p<0.001$) and insulin resistance (77.9% vs. 55.1%, respectively, $p<0.001$) than prepubertal subjects.

The HOMA-IR and ft3 levels were significantly different between subjects with normal and elevated TSH levels (Table 2).

Significant positive correlations were found between TSH and both BMI-SDS ($r=0.146$, $p=0.007$) and HOMA-IR ($r=0.196$, $p<0.001$). The ft3 correlated positively with BMI-SDS ($r=0.202$, $p<0.001$) and negatively with HOMA-IR ($r=-0.126$, $p=0.019$). The ft4 was only significantly correlated with BMI-SDS ($r=0.148$, $p=0.006$). A significant positive correlation was also found between HOMA-IR and BMI-SDS ($r=0.215$, $p<0.001$).

Multiple regression analysis confirmed the relation between TSH, as the dependent variable, and BMI-SDS

Table 2 Association between studied variables and TSH levels.

	Normal TSH	High TSH	p-Value
BMI-SDS	2.9±0.7	3.0±0.5	0.47
ft4, ng/dL	1.1±0.4	4.4±0.7	0.13
ft3, pg/mL	4.1±0.5	4.4±0.7	0.016
HOMA-IR	3.4±2.0	5.0±3.0	0.005

($p=0.018$), after controlling for age, gender, and pubertal state. The bivariate relation between ft4 (dependent variable) and BMI-SDS was also confirmed ($p=0.024$) while ft3 remained unrelated to BMI-SDS ($p=0.07$). Regarding insulin resistance, multiple regression analysis with HOMA-IR as the dependent variable showed significant and independent associations with BMI-SDS ($p<0.001$) and TSH ($p<0.001$) as shown in Figure 1.

Association between variables postintervention

After intervention, 67% of the followed-up children lost weight. Weight loss was significant (BMI-SDS variation ≤ -0.5) in 21% of the sample.

Table 3 shows the characteristics of the intervention group at baseline and after 1 year of lifestyle intervention.

Multiple regression analysis did not show a link between TSH and BMI-SDS variation ($p=0.61$). Nevertheless variations in both TSH and BMI-SDS were significantly and independently associated with HOMA-IR variation ($p=0.005$ and $p=0.016$, respectively), after controlling for age, gender, and pubertal state.

There were no significant differences in Δ TSH during the intervention in relation to the change in BMI-SDS ($p=0.97$). Comparison of subjects' Δ BMI-SDS groups showed significant differences in Δ HOMA-IR ($p=0.008$). Post-hoc analysis showed significant differences between Δ HOMA-IR in the following two groups of Δ BMI-SDS: the (>0) group and the (≤ -0.5) group ($p=0.006$) (Table 4).

Discussion

The prevalence of increased plasma levels of TSH in our sample of obese children and adolescents was 9.3%. Due to the existence of multiple TSH assays and cutoffs it is difficult to directly compare results, but our prevalence is slightly lower than the previously reported value (10%–23%) (1, 3–5, 7, 11, 13, 14, 16, 17). The trend of TSH levels to decrease with age has been previously described (12, 24, 25). Therefore, we chose to use different cutoff values for prepubertal and pubertal children. Shalitin et al. (4) described similar prevalences of hyperthyrotropinemia in prepubertal and pubertal individuals despite having used the same cutoff value in both.

We also found slightly increased ft3 and ft4 concentrations in 4.9% and 11% of the subjects, respectively. These findings are in agreement with other studies in

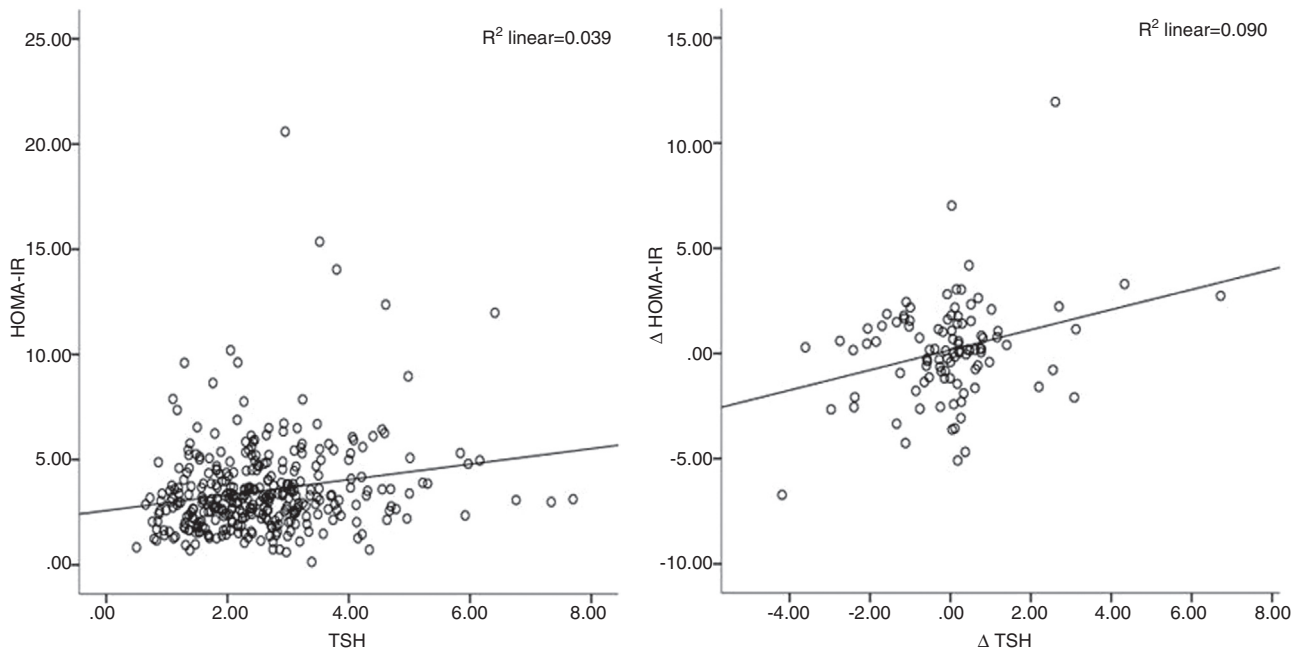


Figure 1 Baseline and postintervention associations between TSH and HOMA-IR.

children and adults, although usually with a greater proportion of elevated fT3 levels than fT4 levels (1, 3, 6, 8, 13, 17, 26). All studied thyroid function parameters showed a significantly positive correlation with BMI-SDS, but only TSH and fT4 remained significant in the regression analysis. These findings are in line with several cross-sectional and longitudinal studies which have found a positive relationship between weight status and thyroid function in obese children (1, 3–6, 9, 11, 13, 14, 16, 27).

To explain the potential defects of thyroid function in obesity several underlying mechanisms have been hypothesized, including iodine deficiency, autoimmune thyroiditis, mutations in the TSH-receptor gene, increased leptin-mediated production of prothyrotropin releasing hormone (TRH), impaired feedback due to a lowered number of T3 receptors in the hypothalamus (thyroid hormone resistance), and variations in deiodinase activity (1, 3, 4, 8). The slight increase in TSH levels is usually not associated with iodine deficiency or autoimmune

thyroiditis (3, 9, 16). Furthermore, nonsynonymous mutations in the TSH-receptor gene are rare (3). Thus, the most favored hypothesis attempting to explain the increased TSH levels in obesity is the increased leptin-mediated production of pro-TRH (3, 6, 9, 28). Leptin stimulates TSH production acting through the hypothalamic-pituitary axis (3, 9, 17). It has been recently reported that leptin signaling, mediated by JAK/STAT pathway, is mandatory for the maintenance of TRH expression in the hypothalamic paraventricular nucleus and thus, for normal production of TSH and thyroid hormones (9, 11, 14, 17, 28). This finding is corroborated by our results, as our obese patients with hyperthyrotropinemia showed significantly higher fT3 values. Furthermore, studies in animal models demonstrate that leptin can decrease deiodinase activity in pituitary tissue, thus modifying the feedback of T3

Table 4 Prepost intervention absolute differences (Δ) of each weight variation group.

	Δ BMC-SDS			p-Value ^a
	>0	-0.5–0	≤-0.5	
n	33	46	21	
Δ TSH, mU/L	0.03±1.81	-0.10±1.22	0.04±1.56	0.97
Δ fT4, ng/dL	-0.07±0.45	-0.07±0.57	-0.04±0.34	0.69
Δ fT3, pg/mL	-0.20±0.43	-0.13±0.55	-0.16±0.57	0.83
Δ HOMA-IR	1.05±2.93	-0.03±1.91	-0.86±1.94	0.008

^aKruskal-Wallis test.

Table 3 Characteristics of the intervention group.

	Baseline	13 year
BMI-SDS	3.0±0.7	2.8±0.7
TSH, mU/L	2.7±1.3	2.7±1.5
fT4, ng/dL	1.2±0.4	1.1±0.5
fT3, pg/mL	4.2±0.5	4.0±0.4
HOMA-IR	3.6±2.0	3.7±2.3

on TSH secretion (3, 8, 9, 28). At the same time, TSH may stimulate leptin production by adipocytes, suggesting a cross-talk between these two hormones (3).

Thyroid hormones are important determinants of glucose homeostasis (1). The influence of insulin resistance, often present in obese patients, on the hypothalamic-pituitary-thyroid axis has been investigated, but conflicting results have been reported (1). The prevalence of HOMA-IR elevation in our sample was nearly 70% and this prevalence was higher among pubertal subjects. We found that obese children with hyperthyrotropinemia had increased insulin resistance and, even within the normal range, TSH and HOMA-IR showed a positive correlation. These findings are in agreement with other studies in adults and children (6, 7, 13, 16, 27, 29). However, it is difficult to prove a causal relationship between thyroid hormones and insulin resistance in obesity as both are influenced by weight status and, after adjustment for BMI, most of these relationships are not significant any longer (1, 6). In our sample, significant bivariate associations were found between thyroid hormones, BMI-SDS, and insulin resistance. The association between TSH and the insulin resistance index remained significant even after adjusting for BMI-SDS.

Experimental studies suggest that thyroid hormones may impact insulin sensitivity by influencing expression or activation of uncoupling protein, β adrenergic receptor, and peroxisome proliferator-activated receptor- γ (27). Contrasting results were reported by other authors who did not detect any association between TSH levels and HOMA-IR (5, 14).

One hundred children completed 1 year of lifestyle modification – 67% of them achieving weight reduction. However, only 21% had a substantial weight decrease, a result that is in line with other reports (1). This result may be the reason why the studied biochemical parameters remained unchanged overall (Table 4). Like several other studies (4, 13, 14, 17, 30) we did not find an association between BMI-SDS variation and TSH, even after substantial weight loss (BMI-SDS variation ≤ -0.5).

Contrary to adults (2, 15, 18, 31–33), the role of thyroid hormones in glucose dysmetabolism in otherwise healthy obese children has been examined to a limited extent. In our pediatric population, both BMI-SDS and TSH variations were independently associated with HOMA-IR variation. Nevertheless, a slight reduction in weight (BMI-SDS decrease <0.5) was not associated with decrease in HOMA-IR, suggesting that a substantial weight reduction is required to modify insulin resistance. A previous study in obese children, in which weight loss significantly reduced

TSH, did not find an association between TSH and changes in insulin sensitivity (11). These data contrast with another study, in which the decrease in TSH, rather than changes in body weight or composition, was the main determinant of improvements in fasting insulin and HOMA-IR (16). Although these data suggest that interventions to decrease TSH concentrations during weight loss in obese subjects could be beneficial in further increasing insulin sensitivity, in the pediatric setting there are no controlled studies looking at outcomes of obese children with elevated TSH levels treated with thyroxine vs. those given placebo (1, 3). The few available data are derived from anecdotal case reports and a small series of cases in which no beneficial effects on body weight, BMI, linear growth, and body lipids were found in treated subjects, suggesting that thyroid substitution is not necessary in most cases (1, 3, 9, 28).

Our study is not without limitations. First, the lack of significant differences of changes in TSH levels during the weight reduction interventions in relation to the change in BMI-SDS may be affected by the small number of participants in each of the subgroups. Second, BMI percentiles were used to classify overweight. Although BMI is a good measure for overweight, it has limitations as an indirect measurement of adiposity. Measurement of body composition would be the ideal. However, the gold standards such as dual-energy X-ray absorptiometer or indirect calorimetry are very difficult to perform in a large group of obese children. Finally, we did not differentiate the effect of diet and increased physical exercise. In contrast to exercise-induced weight loss, diet-induced weight loss has been reported to be associated with changes in thyroid hormone production (34).

In this study, the prevalence of hyperthyrotropinemia was lower than previously reported. Nevertheless, and for the first time, different cutoff values for prepubertal and pubertal children were used, suggesting an over diagnosis of hyperthyrotropinemia in prior studies. At baseline, we found a positive correlation between TSH levels and insulin resistance, independent of body status. One year after the introduction of lifestyle changes, weight loss was related to a significant reduction of HOMA-IR. Although the TSH variation in the weight loss group was not significant, it was associated with the HOMA-IR variation. Whether TSH is responsible for HOMA-IR variations or the opposite is yet to be clarified.

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