The Impact of Adiposity and Puberty on Thyroid Function in Children and Adolescents

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Abstract

Background: In the context of a worldwide increase in childhood obesity, euthyroid hyperthyrotropinemia has been consistently reported and raises questions about its etiology, its potential metabolic complications, and its management. In this study we analyze the thyroid function with respect to BMI, pubertal status, and sex in children with obesity and discuss our results on an integrative context with the existent data from the literature.

Methods: In this case-control study, we compared 389 children and adolescents with obesity to 158 controls. Age, sex, thyroid stimulating hormone (TSH), triiodothyronine (T3), thyroxine (T4), BMI standard deviation score, and pubertal status were recorded. One factor-analysis of variance (ANOVA) was used with $p < 0.05$.

Results: Mean serum TSH of children with obesity was higher (2.95 ± 1.2 mU/L) compared to normal weight group (2.42 ± 1.43 mU/L) ($p < 0.0001$). Only in females of both groups, serum TSH, T4, and T3 concentrations were all lower during puberty compared to prepuberty. In prepubertal girls and boys with obesity, a statistically significant correlation between TSH and BMI was found ($r = 0.32$, $p = 0.012$ and $r = 0.47$, $p < 0.001$, respectively), which is not sustained during puberty.

Conclusions: Our results confirm the TSH elevation in children with obesity and indicates that puberty and adiposity have a differential sex-dependent impact on thyroid axis function.

Keywords: BMI; hyperthyrotropinemia; pediatric obesity; TSH

Introduction

In recent years, accumulating evidence from studies in adults supports that adiposity may cause a mild increase in TSH with normal thyroid hormone levels, which is positively correlated to the degree of adiposity.¹ This euthyroid hyperthyrotropinemia has also been observed in children and adolescents with obesity²⁻⁴ and is usually accompanied by T3 elevation, which is also positively linked to BMI.^{5,6} This is considered to be a result of increased T4 to T3 conversion as a possible adaptive, counter-regulatory mechanism aiming at enhancing basal metabolic rate.⁴

Research on the possible causal relationship between obesity and TSH elevation, using genome-wide association studies, failed to reveal any correlation between known TSH- or fT4-modifying single-nucleotide polymorphism (SNPs) and obesity. This indicates the absence of common thyroid function-affecting and obesogenic SNPs that could genetically connect hyperthyrotropinemia with obesity.⁷

Current literature contains a substantially larger amount of data regarding the metabolic complications of obesity in adolescents. Insulin resistance, the core abnormality of metabolic syndrome, has been found to be independently associated with TSH increase,⁸ and in a rather sexually dimorphic way, since it was observed only in males.⁹ In children and adolescents with obesity, Radetti et al. showed that TSH elevation is associated to higher total cholesterol and increased blood pressure,¹⁰ while Lundback et al. found that TSH was positively associated with fasting insulin, total cholesterol, and triglycerides.¹¹ Anthropometric indices of predominant central obesity such as waist to height ratio are also positively linked to subclinical hypothyroidism¹²; however, no clear association was found between TSH and visceral adipose tissue.¹³ The above data underline the importance of investigating a probable long-term negative impact of TSH elevation on cardiovascular health.

Besides obesity, which seems to have an impact on thyroid axis function, subtle physiological fluctuations of

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thyroid hormone levels have also been described during puberty.^{14,15} Postpubertal values of T4 and T3 were significantly lower than prepubertal ones, in boys and girls, followed by an increase during late puberty.¹⁵ An older study by Michaud et al. on the pubertal variations of plasma TSH, T4, T3, and rT3, in 647 school-age children, found a TSH peak before the clinical onset of puberty followed by T3 and T4 peaks and an increase in T4/rT3 ratio, a state which the authors termed as thyroidarache.¹⁶

Consequently, it seems that thyroid function is influenced by multiple factors, including genetic, developmental, and environmental ones. On the background of a worldwide increase in childhood obesity, this commonly reported euthyroid hyperthyrotropinemia raises issues regarding its physiological significance, its natural course, its metabolic impact, and finally its potential management. In this study, we compared a group of obese children and adolescents to a normal weight age-matched group to characterize their thyroid function in correlation with BMI, sex, and pubertal status.

Subjects and Methods

Subjects

The study groups included 389 children and adolescents with obesity (BMI z-score >2) (Table 1) and 158 healthy age-matched children of normal weight, who served as controls. Subjects with any acute or chronic disease were excluded from the study, as well as all children with positive antibodies against thyroid peroxidase and thyroglobulin. No patient was taking levothyroxine at the time he entered the study.

Methods

This was a case-control study. Date of birth, family history of thyroid disorders, and any acute or chronic disease were recorded. Informed written consent was obtained from the parents of the participating individuals, and the study was approved by the Ethics Committee of “Aghia Sophia” Childrens’ University Hospital.

Height was determined to the nearest centimeter as the average of two measurements using a calibrated Harpenden stadiometer. Weight was measured on a calibrated scale (Seca, model 760) and recorded to the nearest 100 g. Pubertal stage was defined using Tanner’s classification.¹⁷

BMI was calculated using the formula weight/height² (kg/m²). BMI standard deviations score (SDS) was computed for each subject using the formula: BMI-SDS = (actual BMI – mean BMI for age, race, and sex)/BMI SD for age and sex based on the established respective WHO 2007 data.

A blood sample was drawn from all children in the morning from 09.00 to 10.00 h after an overnight fasting. It was centrifuged and the serum was stored at –28°C until assayed.

Hormone Assays and Blood Chemistry

Thyrotropin (TSH) levels were measured by chemiluminescence ILMA two-site Chemiluminescence immunoassay

(Nichols Institute Diagnostics, San Juan Capistrano, CA). The normal range was 0.3–5 mU/L, and the intra- and interassay variability was 3.1% (at 0.51 mU/L) and 2.4% (at 0.13 mU/L), respectively.

Total thyroxine (T4) levels were determined by a radioimmunoassay (RIA) (Brahms; Hennigsdorf, Germany). The normal range was 5–12.8 µg/dL, and the intra- and interassay variability was 2.8% (at 7.2 µg/dL) and 5.1% (at 7.8 µg/dL), respectively.

Total triiodothyronine (T3) levels were measured with RIA (Immunotech, Beckman Coulter Company, Prague, Czech Republic). The normal range was 78.0–182.0 ng/dL, and the intra- and interassay variability was 3% and 8%, respectively.

Statistical Analysis

Correlations were calculated according to Pearson and Spearman, as appropriate. Data are presented as mean ± SD or median as indicated. To compare quantitative variables, one factor-analysis of variance (one-way ANOVA) was used. TSH values were normalized by log transformation. All tests were two-sided. All *p*-values from more than one *t*-test within the same group were corrected with Bonferroni method. The limit of statistical significance was set at *p* < 0.05.

Table 1. Demographic Data and Thyroid Function Measurements		
Groups	Normal weight	Obesity
Individuals	158	389
	Mean ± SD (range)	Mean ± SD (range)
Age	10.3 ± 3.26 (4.8 to 18.4)	10 ± 2.74 (4 to 16)
Males	69	169
Females	89	220
Prepubertal	91	230
BMI z-score all	–0.44 ± 0.76 (–7.37 to 0.77)	3.08 ± 0.80 (2.01 to 8.66)
BMI z-score prepubertal	–0.52* ± 0.9 (–0.70 to –0.33)	3.16 ± 0.09 (2.98 to 3.35)
BMI z-score pubertal	–0.34* ± 0.48 (–0.46 to –0.22)	2.96 ± 0.91 (2.74 to 3.18)
TSH (mU/L)*	2.42 ± 1.20 (0.50 to 6.80)	2.95 ± 1.43 (0.50 to 9.60)
T4 (µg/dL)*	8.38 ± 1.23 (5 to 11.7)	8.86 ± 1.42 (5.10 to 15.50)
T3 (ng/dL)*	178.2 ± 27.70 (104 to 243)	192.1 ± 31.70 (96 to 294)
*Represents statistical significance <i>p</i> < 0.0001. SD, standard deviation; TSH, thyroid-stimulating hormone.		

Table 2. Results of Data Analysis of Thyroid Function in Relation to Sex and Pubertal Status in Children and Adolescents with Normal Weight and Obesity, Respectively

Sex	Pubertal status	Log TSH Mean $\pm$ SD (95% CI)	T4 Mean $\pm$ SD (95% CI)	T3 Mean $\pm$ SD (95% CI)
Normal weight group (n = 158)	Females (89)			
	Prepubertal (44)	0.39 $\pm$ 0.08 (–0.3 to 0.84)	8.84 $\pm$ 1.23 (8.47 to 9.22)	189.5 $\pm$ 17.7 (184 to 194.8)
	Pubertal (45)	0.29 $\pm$ 0.05 (–0.44 to 0.77)	8.01 $\pm$ 1.22 (7.65 to 8.38)	165.1 $\pm$ 31.5 (155.7 to 174.6)
	<i>p</i>	0.047	<0.001	0.003
	Males (69)			
	Prepubertal (47)	0.37 $\pm$ 0.09 (–0.31 to 1.1)	8.51 $\pm$ 1.13 (8.18 to 8.85)	187.4 $\pm$ 26.5 (179.6 to 195.2)
Obesity group (n = 389)	Pubertal (22)	0.34 $\pm$ 0.08 (–0.28 to 0.9)	7.94 $\pm$ 1.15 (8.06 to 8.61)	162 $\pm$ 19.6 (153.2 to 171)
	<i>p</i>	0.228	0.080	0.100
	Females (220)			
	Prepubertal (116)	0.45 $\pm$ 0.2 (0.41 to 0.49)	9.34 $\pm$ 1.38 (9.1 to 9.59)	199.2 $\pm$ 32.7 (193.2 to 205.3)
	Pubertal (104)	0.39 $\pm$ 0.2 (0.35 to 0.43)	8.43 $\pm$ 1.41 (8.15 to 8.71)	186.3 $\pm$ 31.9 (179.9 to 192.6)
	<i>p</i>	0.038	<0.001	<0.001
Males (169)	Prepubertal (114)	0.43 $\pm$ 0.19 (0.4 to 0.47)	8.92 $\pm$ 1.4 (8.66 to 9.19)	191.8 $\pm$ 31.9 (185.7 to 197.9)
	Pubertal (55)	0.4 $\pm$ 0.17 (0.36 to 0.45)	8.52 $\pm$ 1.26 (8.18 to 8.86)	188.5 $\pm$ 26.3 (181.3 to 195.6)
	<i>p</i>	0.510	0.100	0.750

CI, confidence interval.

Bold indicates statistically significant *p* values (*p* < 0.05).

Results

In children with obesity, the mean BMI z-scores of the prepubertal and pubertal subgroups were not significantly different (Table 1) delineating their similar grade of obesity. On the contrary, in the normal weight group, the mean BMI z-score of pubertal children is higher (–0.34) compared with prepubertal children (–0.52) (*p* < 0.0001). The values of TSH, T4, and T3 in the group with obesity are significantly higher than those in the normal weight group (*p* < 0.0001).

The comparison of thyroid axis parameters by pubertal status and sex within the group with obesity and the normal weight group separately shows that in girls of both groups, serum TSH, T4, and T3 concentrations decrease after initiation of puberty compared to the prepubertal period (Table 2). On the contrary, in males, no statistically significant alteration in serum TSH, T3, and T4 concentrations was observed during puberty in both obese and normal weight groups (Table 2). By comparing thyroid function in children and adolescent with obesity, between early puberty (Tanner II) and later stages of puberty (Tanner III–V) we found no significant differences in TSH, T4, and T3 serum values (Supplementary Table S1).

Studying the correlation between thyroid function and adiposity, we found that only within the group with obesity, the TSH was significantly correlated to BMI with coefficients of *r* = 0.32 (*p* = 0.012) in prepubertal males and *r* = 0.47 (*p* < 0.001) in prepubertal females, respectively (Fig. 1). The above statistically significant correlation was no more observed after initiation of puberty, as

assessed by pubertal Tanner stages of ≥ 2 (Fig. 1). In the normal weight group, no correlation between TSH and BMI was found neither before nor after initiation of puberty in both sexes.

Discussion

In this study, we investigated the impact of adiposity and puberty on TSH, T3, and T4 concentrations in children and adolescents of both sexes. Our findings demonstrate that, in accordance with previous studies, children and adolescents with obesity, both prepubertal and pubertal ones, have significantly higher serum TSH, T4, and T3 levels compared with age-matched controls.³

Second, our results show that girls of both obese and normal weight groups demonstrate lower concentrations of TSH and thyroid hormones after initiation of puberty, in concordance with previous report.¹⁵ However, in boys of both groups, no such decrease in TSH and thyroid hormone concentrations was observed, in contrary to existing data.¹⁵ These sex-specific TSH associations with different indices of metabolism have been also supported by other studies. Javed et al. found a male specific negative correlation between TSH and insulin sensitivity, and Minami et al. reported positive correlations of TSH with levels of glucose, diastolic blood pressure, and nonhigh density lipoprotein and cholesterol in girls.^{9,18}

Merging the above observations with our data, we consider that sex hormones may have a role in the regulation of

Figure 1. Correlation of BMI z-score to log TSH in females and males according to Tanner stages.

the hypothalamic-pituitary-thyroid (HPT) axis. The increase of estrogen levels in girls during puberty may exert a suppressive action directly or indirectly, either on the hypothalamic or the pituitary level, to lower the set point of the HPT axis. Alternatively, a primary effect of estrogen on the thyroid gland could also be present. Except from the well-known indirect effects of estrogens on the thyroid hormone bioavailability through the increase of thyroid hormone binding globulin,¹⁹ a number of studies have shown that estradiol exerts a direct effect on the thyroid gland. Expression of both isoforms of estrogen receptors (*ERα* and *ERβ*) has been reported on both normal and neoplastic thyroid tissue.^{20,21}

Furthermore, several studies have described proliferation of cells induced by estradiol.^{22–24} Nongenomic action of estradiol through binding to the intracellular G-coupled protein receptor 30 may also contribute to the above proliferative effect as it has been also found to be expressed in thyroid cancer cells,²⁵ and basic studies have shown a decrease of the sodium–iodide symporter (NIS) gene expression and iodide uptake induced by estrogen action.^{26,27} All of the above-described actions of estradiol on the molecular level may therefore have either raising or lowering effect on the HPT set point. In conclusion, it seems that there is a sex dimorphic effect of puberty on thyroid function irrespective of weight status.

An important link between adiposity and thyroid metabolism is leptin, an adipocyte-derived hormone, which is involved in tuning the energy balance and in the regulation of food intake by providing inhibitory signals to the hypothalamus.²⁸ At the molecular level, leptin activates the Janus kinase/signal transducer and activator of transcription 3 intracellular signaling pathway by binding to its receptor (LepR). Increased fat mass and BMI in obesity are associated with an increased secretion of leptin.²⁸ Previous studies have demonstrated a positive correlation between BMI and serum TSH, as well as a positive correlation between weight gain during 5 years and a progressive increase in serum TSH values.^{29,30} It has been hypothesized that leptin increases the

production of pro-TRH in the hypothalamus and therefore increases TSH levels.³¹ Leptin has also been positively associated with TSH, independent of BMI.³²

The associations obtained from the analysis of our data could fit into an interaction model between adiposity, pubertal status, and HPT axis set point. All females, with and without obesity, show a decrease in HPT axis set point after initiation of puberty indicating an overall estrogen-mediated lowering effect. In addition, interestingly, while there is a positive correlation in the prepubertal obese girls between BMI and TSH, this correlation is not sustained after initiation of puberty. Pubertal levels of estradiol could be responsible for this dissociation between BMI and TSH by obtunding the leptin-mediated increase in TSH.

In males, the main source of estrogens is the peripheral aromatization of androgens in the adipose tissue. Males with obesity through the increased adiposity demonstrate elevated estradiol concentration, as well as increased leptin.⁶ In our male population the set point of HPT axis does not seem to be affected by puberty in both normal and obese subgroups. On the contrary, the link between BMI and TSH follows the same pattern as in females, with absence of correlation after initiation of puberty. It can be postulated that elevated estradiol in obese males may be enough to suppress the TSH increasing effect of leptin but inadequate to lower the HPT axis set point during and after puberty.

In conclusion, the hyperthyrotropinemia reported in children and adolescents with obesity seems to prevail mostly in prepubertal children, where a clear correlation of TSH to BMI is observed, while during puberty there is a sexually dimorphic effect with subtle alterations in the HPT set point observed only in females and loss of TSH to BMI association in both sexes. Further studies investigating estradiol and leptin in children with obesity in correlation to thyroid function will be able to assess the validity of the above-mentioned observations and provide clinicians a more integrated perspective in evaluating and managing the thyroid axis variations in children and adolescents with obesity.

Author Disclosure Statement

No competing financial interests exist.

Informed written consent was obtained from the parents of the participating individuals, and the study was approved by the Ethics Committee of “Aghia Sophia” Childrens’ University Hospital, Athens, Greece.

Supplementary Material

Supplementary Table S1

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