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ORIGINAL ARTICLE

The relationship between hyperthyrotropinemia and metabolic and cardiovascular risk factors in a large group of overweight and obese children and adolescents

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Abstract
Purpose Mild TSH elevations are frequently observed in obese patients, in the absence of any detectable thyroid disease. Our objective is to evaluate the relationship between the raised TSH levels and the biochemical and clinical consequences of obesity.
Methods This is a retrospective cross-sectional study of a large population of obese children and adolescents. We evaluated 833 subjects (340 m, 493 f), aged 14.4 ± 2.5 (range 5.2–18.5) years, height SDS 0.27 ± 1.04 (−3.49–4.35), and BMI SDS 2.94 ± 0.59 (1.60–4.68). Body composition, free T4, TSH, anti-TPO antibodies, anti-TG antibodies, inflammation markers (total WBC and the subtypes, ultrasensitive C-reactive protein), and metabolic parameters [AST, ALT, γGT, ALP, glycaemia, insulin, total cholesterol (TC), HDL-cholesterol (HDL-C), and LDL-cholesterol (LDL-C), triglycerides (TG)] were measured, and oral disposition index (ODI) and cardiovascular risk factors (TC/HDL-C and TG/HDL-C) were calculated. After exclusion of the subjects showing anti-thyroid antibodies, the remaining 779 (325 m, 454 f) were then subdivided into two subgroups according to a TSH value below (group A) or above (group B) 4.5 mU/L.
Results Clinical characteristics and hematological markers of patients with and without positive anti-thyroid antibodies were similar, with the exception of higher TSH levels in the latter group. Using analysis of covariance, the subjects of group B had significantly higher values of TC (170.3 ± 28.7 vs 163.3 ± 32.9 mg/dL; $p < 0.05$), systolic (125.8 ± 13.5 vs 124.5 ± 13.1 mm/Hg), and diastolic blood pressure (79.2 ± 8.0 vs 77.9 ± 8.2 mm/Hg) than subjects of group A. No difference was observed in body composition, ODI, and the cardiovascular risk factors between these two groups.
Conclusion TSH elevation in overweight and obese children and adolescents, being associated with a higher TC and blood pressure, might negatively influence the cardiac status. Longitudinal studies are requested, however, to confirm this hypothesis and, therefore, to conclude whether a substitutive treatment with l-thyroxine is really needed in these patients.

Keywords Hyperthyrotropinemia · Obesity · Cardiovascular risk factors · Children · Adolescent

Introduction

Obese patients, even in the absence of any thyroid disease, frequently show alterations of thyroid function, which are now considered more a consequence than the cause of obesity. In fact, these abnormalities usually normalize after weight loss, whether the loss is obtained with diet or bariatric surgery [1–6], suggesting that the underlying cause is functional and reversible.

Thyroid hormones and TSH concentration have been variously described as normal, elevated or even low in obese subjects as compared to normal weight controls

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[1, 7–12]. High serum TSH and normal thyroid hormone concentration have been reported in obese children as well [1, 2, 13–15]. Moreover, it has been shown that thyroid structure is also altered in overweight/obese children [14], similarly improving after weight loss [15]. Although the real cause for the hyperthyrotropinemia (HTSH) is still unknown, several mechanisms have been hypothesized, including increased leptin-mediated production of pro-TRH [16–18], impaired feedback due to a lowered number of T3 receptors in the hypothalamus [19] and variations in peripheral deiodinase activity [18, 19]. Other potential mechanisms might be the adaptive process to increase energy expenditure, the presence of insulin resistance, and chronic low-grade inflammation [20].

A further important point is whether the morbidities frequently associated with obesity, such as an impaired glucose tolerance [21] and, furthermore, the metabolic syndrome (MetS) [22], might be negatively influenced by the concomitant presence of HTSH. In this light, a population-based, cross-sectional study of children and adolescents has previously reported a positive association between higher TSH levels and less favorable lipid levels [23]. Data about this issue, however, are still conflicting. No significant association between serum TSH levels and the presence of MetS has been reported in obese and overweight adults [24]. By contrast, other authors have shown in a group of 260 obese children and adolescents that TSH levels may affect the occurrence of MetS, but not all of the MetS parameters [25]. In this study, we retrospectively examined a large number of overweight obese children and adolescents, with different thyroid status to evaluate the relationship between HTSH and the biochemical and clinical consequences of weight excess.

Methods

Study population

Between March 2004 and December 2007 we evaluated 833 overweight and obese children [340 males, 493 females, aged 14.4 ± 2.5 (5.2–18.5) years, height standard deviation score (SDS) 0.27 ± 1.04 (−3.49–4.35), and body mass index (BMI = kg/cm^2) SDS 2.94 ± 0.59 (1.60–4.68)], consecutively enrolled in the obesity outpatient clinic of the Istituto Auxologico Italiano. 801 subjects (322 males, 479 females) fulfilled the criteria for obesity (BMI SDS > 2) (96.1%), while 32 (18 males, 14 females) were overweight (BMI SDS between 1.4 and 2.00) (3.9%). All the subjects were born full-term and suffered from simple obesity, other syndromic, organic and hormonal causes having been excluded. Obese and overweight patients were subdivided between subjects with (Ab+) and without (Ab−) anti-thyroid antibodies (TPOAbs and/or TGAbs), and compared with each other. To exclude the interference of primary thyroid abnormalities on the relationship between HTSH and obesity-associated comorbidities, the Ab+ subjects were then excluded, and the Ab− patients were subdivided into group A (TSH < 4.5 U/mL and normal fT4) and group B (TSH > 4.5 but < 10 U/mL and normal fT4).

The study protocol was approved by the Ethical Committee of the Istituto Auxologico Italiano. Written informed consent was obtained for all procedures from parents or legal guardians and written assent from children and adolescents were obtained before enrolment.

Anthropometric measurements

The subjects were admitted to the ward following overnight fasting. Physical examination was carried out by the same investigators specifically trained. Standing height was determined by a Harpenden Stadiometer (Holtain Limited, Crymych, Dyfed, UK). Body weight was measured to the nearest 0.1 kg, using standard equipment. The published Italian standards for age- and gender-specific weight, height, and BMI percentiles were used for calculating SDS [26]. Waist circumference (WC) was determined at the midpoint between the lowest costal ridge and the upper border of the iliac crest, and hip circumference (HC) was measured at the largest circumference between waist and knee. The waist to hip ratio (W/H) was then calculated as well as the waist to height ratio (W/Hr), which is reported to be an index of metabolic risk [27], was calculated. Pubertal development was assessed according to Tanner staging [28].

Laboratory analyses

Blood samples were obtained for assessment of fT4, TSH, TPOAbs, and TGAbs. As inflammation markers, total leucocytes and the subtypes [29], the neutrophil:lymphocyte ratio (NLR) [30, 31], and C-reactive protein were evaluated. Metabolic parameters included glycaemia, insulin, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl-transferase (γGT), and alkaline phosphatase (ALP). Because of the association with liver steatosis, the AST/ALT ratio was evaluated [32]. The atherogenic index (TC/HDL-C) and the TG/HDL-C ratio, which are considered indexes of severe cardiovascular risk [33, 34], were also calculated.

In all patients, a standard oral glucose tolerance test (1.75 g of glucose/kg body weight up to 75 g with blood

samples taken at 0, 30, 60, 90, 120 min) was then performed to evaluate glucose and insulin homeostasis.

Insulin sensitivity (HOMA-S) and insulin resistance (HOMAr) were evaluated in the basal state, by use of the homeostatic model assessment: HOMA-S = 1/{[(insulin (uIU/mL) × glucose (mg/dL)]/22.5}; HOMAr = [insulin (μU/mL) × blood glucose (mmol/L)/22.5] [35].

Insulin secretion was assessed with the insulinogenic index (IGI), which is the ratio of the changes in insulin (I) and glucose (G) concentration from 0 to 30 min (ΔI0–30/ΔG0–30) [36].

ß-cell compensatory capacity to change insulin sensitivity was evaluated by the oral disposition index (ODI) and defined as the product of HOMA-S and IGI [37].

Assays

TSH was measured by a chemiluminescent immunometric assay (Roche Diagnostics GmbH, Manheim, Germany); the intra- and inter-assay C.V. were 2.7 and 3.2%, respectively, and sensitivity limit was 0.005 mU/L. Measurement of fT4 was performed by chemiluminescent immunometric assay (Roche Diagnostics GmbH, Manheim, Germany); the intra- and inter-assay C.V. were 1.8 and 2.6%, respectively, and sensitivity limit was 0.3 pmol/L. Thyroglobulin antibodies (TG-Ab) were measured by a chemiluminescent immunometric assay (Immulite 2000 Anti-TG Ab, DPC, LA, USA) with an intra- and inter-assay C.V. of 3.2 and 4.6%, respectively, and sensitivity limit of 2.2 U/mL; thyroid peroxidase antibodies (TPO-Ab) were measured by chemiluminescent immunometric assay (Immulite 2000 Anti-TG Ab, DPC, LA, USA) with an intra- and inter-assay C.V. of 5.2 and 3.2%, respectively, and sensitivity limit of 5 U/mL.

Leukocyte, neutrophil, and lymphocyte counts were carried out using the automated hematology analyzer. Then, by dividing the neutrophil by the lymphocyte count, we calculated the NLR. ALT, AST, γGT, and ALP were measured by a Hitachi 917 Analyzer and Roche Diagnostics reagents (both Mannheim, Germany).

Ultrasensitive C-reactive protein (CRP) was measured by HS Roche kit using Cobas Integra 800 (Roche Diagnostics).

Serum insulin levels were measured by chemiluminescence (Immulite 2000). Enzymatic methods (Roche Molecular Biochemicals, Mannheim, Germany) were used for determination of blood glucose, TC, HDL-C, LDL-C, and TG.

Blood pressure measurements and instrumental examination

Diastolic and systolic blood pressure (BP) was measured to the nearest 2 mmHg in the supine position after 5-min rest, using a standard mercury sphygmomanometer with appropriate-sized cuff. The average of three measurements on different days was used.

Body composition, expressed as fat mass percentage (FM%) and fat-free mass percentage (FFM%), was assessed by bioelectrical impedance analysis (BIA) using a tetrapolar impedance meter (Human-IM Scan; DS-Medigroup, Milan, Italy). FFM has been calculated using to the prediction equation developed by Lazzer et al. [38]. Measurements were performed according to the method of Lukaski et al. [39], after 20-min rest in a supine position with relaxed arms and legs. Immediately after assessment of body composition, basal metabolic rate (BMR) was determined by means of open-circuit, indirect computerized calorimetry (Vmax 29; Sensor Medics, Yorba Linda, CA, USA) with a rigid, transparent, ventilated canopy. Patients remained at rest in the supine position for 10 min to achieve steady state, and then BMR (expressed as Kcal/day) was measured for 30 min.

Definitions

The BMI cutoff point of >2 SDS was used to define obesity, and between 1.4 and 2 SDS for overweight [26].

TSH value within the reference range was considered normal; HTSH was defined in the presence of serum TSH values between 4.5 and 10 mU/L, with serum fT4 within the reference range. CRP reference value was less than 0.5 mg/dL.

Diagnosis of altered glucose metabolism was determined according to the American Diabetes Association criteria [40]. Hypertension was defined as values of systolic or diastolic BP >95th percentile for age, sex, and height [41] or when any antihypertensive drug was being used.

According to the IDF criteria for MetS diagnosis in children and adolescents [42], our patients were considered to have the MetS (Mets-IDF) if they had abdominal obesity (WC ≥90th percentile for ages <16 years, and ≥94 cm for males and ≥80 cm for female for ages >16 years) plus two or more of the following factors [1]: raised TG level: ≥150 mg/dL (1.7 mmol/L) for ages <16 years and the same cutoff or specific treatment for this lipid abnormality for ages >16 years [2]; reduced HDL-C: <40 mg/dL (1.03 mmol/L) for males and females for ages <16 years, and <40 mg/dL for males and <50 mg/dL (1.29 mmol/L) for females, or specific treatment for this lipid abnormality for ages >16 years [3]; raised BP: systolic BP ≥130 mmHg or diastolic BP ≥85 mmHg for ages <16 years, and same cutoff or treatment of previously diagnosed hypertension for ages >16 years [4]; raised FPG concentration ≥100 mg/dL (5.6 mmol/L) or previously diagnosed type-2 diabetes for all ages.

However, the classification of MetS according to IDF criteria could result in the loss of some information. In this light, it has been suggested to establish the prevalence using the percentile distributions of the individual MetS components [43]. Consequently, for patients between 6 and 14 years of age a symmetric criterion for age- and gender-wise percentile's definitions of abnormalities among the MetS diagnostic criteria was adopted >90th for WC, TG, FPG and BP (systolic and/or diastolic), and <10th for HDL-C, as proposed by Martino et al. [44]. MetS was diagnosed in the presence of any combination of three out of five abnormalities (MetS-PERC).

Statistical analysis

Statistical evaluations were performed with the software SAS Enterprise Guide 2006 4.3 (SAS Institute Inc., Cary, NC, USA). All the data are expressed as mean ± SD. For descriptive analysis, the differences between the different groups were assessed using the Student *t* test.

For comparisons between TSH groups we used models of analysis of covariance, with the variables of interest as dependent, the TSH group as factor, and age and BMI SDS as covariates. This would allow adjusting for age/puberty and degree of adiposity. With Tanner stage as dependent we used generalized linear models (multinomial model with cumulative-logit link), age and BMI SDS as covariates and the TSH group as factor.

Results

Clinical characteristics (Table 1)

The group with positive anti-thyroid antibodies (Ab+) included 54 patients (6.5%) (3 overweight and 51 obese), while the group negative for anti-thyroid antibodies (Ab−) consisted of 779 subjects (93.5%) (31 overweight and 748 obese). The clinical characteristics of the two study groups were similar.Subjects of group A (TSH < 4.5 mU/L) were older ($p < 0.01$) and with a more advanced pubertal development than those of group B (TSH > 4.5 mU/L) ($p < 0.005$), which, however, were taller ($p < 0.05$). No difference was observed in terms of BMI SDS, BP, waist to hip ratio, and waist to height ratio. In both groups, the percentage of overweight and obese was very similar (group A: 3.6 vs 96.4%; group B: 3.4 vs 96.6%).

Hormonal, inflammatory parameters, and lipid profile (Table 2)

TSH levels and NLR were significantly higher in the group with positive anti-thyroid antibodies in comparison to

Table 1 Clinical characteristics of (1) patients with (Ab+) and without (Ab−) anti-thyroid antibodies, and (2) Ab− patients with TSH < 4.5 mU/L (group A) or TSH > 4.5 mU/L (group B)

	Groups	# pts	Male	Female	Age (year)	Tanner stage	Height SDS	Weight SDS	BMI SDS	SBP (mmHg)	DBP (mmHg)	W/H	W/Hr
(1)	Ab+	54	15	39	14.8 ± 2.1	3.87 ± 1.36	0.26 ± 1.01	3.06 ± 0.91	2.96 ± 0.60	124.8 ± 7.7	77.6 ± 5.8	0.95 ± 0.08	0.71 ± 0.09
	Ab−	779	325	454	14.4 ± 2.6	3.65 ± 1.48	0.27 ± 1.04	3.02 ± 0.84	2.94 ± 0.59	124.7 ± 13.2	78.1 ± 8.2	0.95 ± 0.08	0.70 ± 0.08
	p				NS	NS	NS	NS	NS	NS	NS	NS	NS
(2)	Group A	654	267	387	14.5 ± 2.5	3.72 ± 1.45	0.24 ± 1.04	3.02 ± 0.84	2.94 ± 0.59	124.5 ± 13.1	77.9 ± 8.2	0.95 ± 0.08	0.70 ± 0.08
	Group B	125	58	67	13.8 ± 2.7	3.27 ± 1.59	0.45 ± 1.01	3.05 ± 0.86	2.93 ± 0.61	125.8 ± 13.5	79.2 ± 8.0	0.95 ± 0.08	0.70 ± 0.08
	p				<0.01	<0.005	<0.05	NS	NS	NS	NS	NS	NS

The statistical analysis was performed with student's *t* test

SBP systolic blood pressure, *DBP* diastolic blood pressure

Table 2 Hormonal, inflammatory parameters, lipid profile, and liver enzymes of (1) patients with (Ab+) and without (Ab−) anti-thyroid antibodies, and (2) Ab− patients with TSH < 4.5 mU/L (group A) or TSH > 4.5 mU/L (group B)

	Groups	Free T4 pg/mL	TSH µIU/mL	PCR mg/dL	Leucocytes/mmc	NLR	Triglycerides mg/dL	Total-C mg/dL	HDL-C mg/dL	LDL-C U/L	ALP U/L	AST U/L	ALT U/L	AST/ALT ratio	γGT U/L	TGAbs kU/L	TPOAbs kU/L
(1)	Ab+	11.6 ± 2.2	4.5 ± 3.7	0.52 ± 0.59	8.66 ± 2.20	1.69 ± 0.87	95.8 ± 32.9	168.9 ± 24.5	43.7 ± 11.7	108.1 ± 25.1	140.3 ± 78.3	22.5 ± 7.9	26.9 ± 16.8	0.95 ± 0.29	18.2 ± 8.7	374 ± 755	256 ± 320
	Ab−	11.7 ± 1.9	3.2 ± 1.5	0.57 ± 0.78	8.41 ± 1.88	1.46 ± 0.60	94.9 ± 40.5	164.4 ± 32.4	43.3 ± 11.0	104.2 ± 29.5	152.4 ± 88.3	22.9 ± 10.1	29.4 ± 23.7	0.93 ± 0.31	19.7 ± 14.3	14.8 ± 7.1	8.3 ± 5.6
	p	NS	<0.001	NS	NS	<0.005	NS	NS	NS	NS	NS	NS	NS	NS	NS	<0.0001	<0.0001
(2)	Group A	11.7 ± 1.9	2.7 ± 0.9	0.56 ± 0.74	8.42 ± 1.91	1.47 ± 0.62	93.9 ± 40.3	163.3 ± 32.9	43.1 ± 10.9	103.5 ± 30.1	149.3 ± 87.7	22.5 ± 9.6	28.9 ± 22.2	0.93 ± 0.30	19.8 ± 14.4	14.7 ± 6.2	8.4 ± 5.6
	Group B	11.7 ± 1.9	5.7 ± 1.0	0.63 ± 0.99	8.35 ± 1.77	1.38 ± 0.51	99.7 ± 40.8	170.3 ± 28.7	44.7 ± 11.8	108.1 ± 25.7	168.6 ± 89.7	24.8 ± 12.2	32.1 ± 30.1	0.95 ± 0.34	19.3 ± 13.7	15.5 ± 10.7	8.2 ± 5.3
	p	NS	<0.001	NS	NS	NS	NS	<0.05	NS	NS	<0.05	<0.05	NS	NS	NS	NS	NS

The statistical analysis was performed with student's *t* test

patients with negative anti-thyroid antibodies, with no difference in the remaining parameters.As expected, TSH was significantly higher in group B than in group A, while fT4 was similar in the two groups. The inflammatory parameters were also similar in the two groups. Subjects of group B showed significantly higher values of ALP (168.6 ± 89.7 vs 149.3 ± 87.7 U/L; $p < 0.05$), TC (170.3 ± 28.7 vs 163.3 ± 32.9 mg/dL; $p < 0.05$), and AST (24.8 ± 12.2 vs 22.5 ± 9.6 U/L; $p < 0.05$) than those of group A. There was no difference between the two groups for γGT, ALT, and AST/ALT ratio, as well as for the other metabolic markers.

Calorimetry, body composition, glucose homeostasis, and cardiovascular risk factors in group A and in group B (Table 3).

No difference among the different parameters was observed. In addition, BMR normalized by FFM was similar in the two groups (data not shown). A higher prevalence of MetS was found when using percentile's cutoffs than IDF criteria ($p < 0.05$).

Analysis of covariance

The analysis of covariance of the inflammatory parameters, lipid profile, calorimetry, body composition, glucose homeostasis, and cardiovascular risk factors, after adjusting for age/puberty and degree of adiposity showed that TC, systolic BP, and diastolic BP were the only parameters significantly higher in group B ($p < 0.05$).

Discussion

In this study, we aimed to retrospectively investigate in a group of overweight and obese children and adolescents the relationship between the raised TSH, which is commonly encountered in these subjects, with body composition, BMR, inflammation markers, liver parameters, glucose homeostasis, the presence of MetS, and of cardiovascular risk factors. In this light, subjects with anti-thyroid antibodies were excluded to avoid the potential effect of primary thyroid alterations on the interrelationship between HTSH and obesity-related comorbidities. However, no difference was detected between subjects with and without anti-thyroid antibodies, with the exception of higher TSH levels in the Ab+ group, probably as early expression of thyroid damage.

The patients without anti-thyroid antibodies were subdivided into two groups on the basis of their TSH values (less or more than 4.5 mU/L—but lower than 10 mU/L). The major strength of our study was the very large sample of overweight and obese subjects recruited, which gave us the chance to do robust statistical analyses.

Table 3 Calorimetry, body composition, glucose homeostasis, and cardiovascular risk factors in group A (TSH < 4.5 mU/L) and in group B (TSH > 4.5 mU/L)

	Calorimetry Kcal/day	FFM%	FM%	Mets-IDF%	MetS-PERC%	DMT2%	IGT%	HOMA-IR	HOMA-S	IGI $\Delta I_{0-60}/\Delta G_{0-60}$	ODI	TG/HDL	CT/HDL
Group A	1904.5 ± 375.3	46.7 ± 9.3	51.9 ± 15.3	25	34	0.6	15.3	2.88 ± 1.84	0.56 ± 5.0.50	1.6 ± 1.6	0.7 ± 0.8	2.38 ± 1.37	3.99 ± 1.17
Group B	1897.3 ± 434.2	45.8 ± 7.9	50.4 ± 14.7	28	40	0	11.2	3.02 ± 1.71	0.56 ± 0.73	1.70 ± 1.21	0.80 ± 1.33	2.50 ± 1.50	4.05 ± 1.25
p	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS

The statistical analysis was performed with student's *t* test

As previously reported in adult patients [45], no difference in body composition, evaluated by BIA, was observed according to the TSH levels. BIA is considered a useful tool to objectively determine even subtle manifestations of thyroid disease [46], although thyroid function seems to affect body composition only when thyroxine concentrations fall below the normal range [7]. BMR, evaluated by indirect computerized calorimetry, showed similar values in group A and group B. Whereas hypothyroid subjects have a decreased BMR, it is unknown whether BMR is associated with TSH in euthyroid subjects. Our data confirmed the results of previous studies performed in adult population, both in overweight [47] and in obese subjects [45].

Chronic low-grade inflammation is characteristic of obesity and, in fact, elevated mean CRP levels were found in our subjects when compared to the normal values. However, inflammation markers, including CRP, were comparable in subjects with TSH less or more than 4.5 mU/L, confirming the lack of correlation between TSH elevation and the increased CRP level in patients with different thyroid status [48].

Higher AST and ALP values were found in group B. The former might suggest a higher degree of hepatic steatosis; however, ALT, AST/ALT ratio, and γGT values, which better correlate with liver damage [32], were not different in the two groups, therefore, making this hypothesis unreliable. The higher ALP levels might be a marker of a larger adipose tissue in the group with HTSH. In fact, ALP is secreted by the adipose tissue [49] and its serum level is considered to mirror an enhanced secretion and amount of adipocytes in obese subjects [50]. Body composition was, as a matter of fact, very similar in the two groups, thus excluding this assumption. However, when the data were re-analyzed with the analysis of covariance, after adjusting for age/puberty and degree of adiposity the AST and ALP values were no more different between the two groups. Therefore, the interpretation of higher values of both AST and ALT in patients with HTSH deserves further studies.

The present study failed to detect any difference in MetS prevalence, depending on TSH levels. Moreover, our results confirmed that MetS diagnosis is largely dependent on the criteria adopted, since its prevalence was significantly higher using MetS-PERC than MetS-IDF.

By descriptive analysis, groups A and B did not significantly differ for the metabolic parameters, the glucose homeostasis, BMR, and the cardiovascular risk factors, while group B showed significantly higher TC than group A. Using analysis of covariance, higher TC values as well as a significant higher systolic and diastolic BP were found in group B, in agreement with the results previously reported by another group [23, 51].

Higher BP, which is often encountered in prepubertal obese children [52], is strongly involved in the pathogenesis of cardiovascular diseases [53]. According to our results, a HTSH state would even worsen the negative influence of weight excess. However, our data are derived from a cross-sectional study and since association does not mean causality, a longer longitudinal survey is needed to verify this hypothesis, as previously suggested [54].

The increased serum cholesterol in our HTSH subjects would put them in a high-risk metabolic situation; however, the primary role of cholesterol in the cardiovascular disease has been recently questioned. Contrary to prevailing literature, in fact, systematic reviews and meta-analyses showed no excess of cardiovascular risk associated with the intake of saturated fat [55]. Moreover, available evidence from randomized controlled trials did not support the hypothesis that a serum cholesterol-lowering diet translates into a lower risk of death from coronary heart disease or all-cause mortality [56, 57].

As a matter of fact, the meaning of our findings will be clarified only by longitudinal studies, but meanwhile the high blood pressure found in our children and adolescents suggest the need for a particular care and follow-up of these patients.

If the hypothesis that a prolonged state of HTSH might negatively influence the blood pressure and, therefore, the cardiovascular function is be confirmed, this would challenge the current recommendations that in the presence of a normal fT4 serum TSH should reach at least 10 mU/L to consider a substitutive treatment [58].

However, there is no evidence from the adult literature that HTSH is a cause of cardiac dysfunction [59] nor that there is an improvement in survival or cardiovascular morbidity following L-T4 therapy, apart from some beneficial effects on lipid profiles and left ventricular function [60]. In addition, the long-term impact of levothyroxine on metabolic outcomes in HTSH children remains still unclear [61].

In conclusion, obese children and adolescents with a mildly elevated TSH show high cholesterol levels and raised blood pressure, both of which might negatively influence the cardiovascular function. Longitudinal studies are strongly requested to verify this hypothesis and, therefore, to conclude whether a substitutive treatment with l-thyroxine is really needed in these patients.

Compliance with ethical standards

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

Ethical approval The study protocol was approved by the Ethical Committee of the Istituto Auxologico Italiano.

Informed consent Written informed consent was obtained for all procedures from parents or legal guardians and written assent from children and adolescents were obtained before enrolment.

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