Association Between Thyrotropin Levels and Insulin Sensitivity in Euthyroid Obese Adolescents

Asma Javed,¹ P. Babu Balagopal,² Adrian Vella,³ Philip R. Fischer,⁴ Francesca Piccinini,⁵ Chiara Dalla Man,⁵ Claudio Cobelli,⁵ Paula D. Giesler,⁶ Jeanette M. Laugen,⁶ and Seema Kumar¹

Background: Thyrotropin (TSH) levels display a positive association with body mass index (BMI), and the prevalence of isolated hyperthyrotropinemia is higher in obese adolescents compared to their normal weight controls. However, the metabolic significance of the higher TSH in obese adolescents is less clear. The objective of this study was to determine the relationship between TSH concentrations and insulin sensitivity, lipids, and adipokines in euthyroid, non-diabetic, obese adolescents.

Methods: Thirty-six euthyroid, non-diabetic, obese adolescents between the ages of 12 and 18 years underwent a 75 g oral glucose tolerance test. Insulin sensitivity (S_i) and pancreatic β -cell function as assessed by disposition index (DI) were measured using the oral glucose minimal model approach. Cholesterol (total, low-density lipoprotein [LDL-C], and high-density lipoprotein [HDL-C]), triglycerides (TG), interleukin-6 (IL-6), total and high molecular weight (HMW) adiponectin, and retinol binding protein-4 (RBP4) were also determined. Associations between measures of thyroid function and S_i , DI, lipids, and adipokines were computed using Pearson's correlation coefficient and multiple regression analysis.

Results: The mean age of the subjects was 14.3 ± 1.88 years, and the mean BMI was 32.5 ± 4.65 kg/m²; 97% were non-Hispanic white and 47% were male. The mean TSH was 2.7 ± 1.2 mIU/L. Increasing serum TSH was correlated with decreasing S_i (log S_i) in the entire cohort ($p=0.03$), but this relationship persisted only in males ($p=0.02$). The correlation between TSH and S_i in males remained significant after adjusting for BMI ($p=0.02$). There was no correlation between TSH and pancreatic β -cell function as assessed by DI ($p=0.48$). TSH correlated positively with LDL-C ($p=0.04$) and IL-6 ($p=0.03$), but these associations vanished or weakened after adjusting for BMI (LDL-C p -value=0.44; IL-6 p -value=0.07).

Conclusions: This study suggests a sex-specific association between TSH and insulin sensitivity in euthyroid, non-diabetic, obese adolescent males. Prospective studies are warranted to explore further this sexual dimorphism in the relationship between thyroid function and insulin sensitivity and to determine if obese adolescents with insulin resistance receiving thyroid supplements for hypothyroidism would benefit from targeting TSH levels in the lower half of normal range.

Introduction

THERE IS SIGNIFICANT CONTROVERSY on the cutoff values to distinguish between a normal and elevated level of thyrotropin (TSH) (1,2). Levels of TSH positively correlate with body mass index (BMI) and have been shown to be higher in obese children compared to normal weight children (3,4). A significant proportion of overweight and obese ad-

olescents demonstrate the metabolic syndrome characterized by insulin resistance and dyslipidemia (5,6), and even TSH levels within the normal range in children have been shown to correlate with insulin resistance indices, such as homeostasis model assessment-estimated insulin resistance (HOMA-IR), and serum triglyceride (TG) levels (3,7,8).

In euthyroid adults, TSH is positively associated with fasting and postprandial insulin concentration and negatively

¹Division of Pediatric Endocrinology, Department of Pediatric and Adolescent Medicine; ³Division of Endocrinology and Metabolism, Department of Internal Medicine; ⁴Division of General Pediatric and Adolescent Medicine, Department of Pediatric and Adolescent Medicine; ⁶Endocrine Research Unit, Division of Endocrinology, Diabetes, Metabolism, and Nutrition, Department of Internal Medicine; Mayo Clinic, Rochester, Minnesota.

²Nemours Children's Clinic, Research Division, Jacksonville, Florida.

⁵Department of Information Engineering, University of Padua, Padua, Italy.

associated with insulin sensitivity calculated following an oral glucose tolerance test (9,10). Moreover, low normal free thyroxine (fT4) levels are significantly associated with increased insulin resistance calculated using HOMA-IR (11).

The data in children on the association between thyroid function and insulin sensitivity are currently limited to surrogate markers of insulin sensitivity derived from fasting parameters such as glucose and insulin.

Adipose tissue dysfunction in obesity leads to derangements in the turnover and function of various biologically active molecules, including adiponectin, retinol binding protein-4 (RBP4), and interleukin-6 (IL-6) (12–16). Thyroid function has been shown to influence adipocyte metabolism and the production of various adipokines (17–19).

The primary objective of the current study was to determine the association between TSH and insulin sensitivity in euthyroid, non-diabetic, obese adolescents. The relationship was also examined between thyroid function and pancreatic β -cell function, lipids, and adipokines in adolescents.

Methods

Participants

The study participants were euthyroid, non-diabetic, obese adolescents who participated in a randomized clinical trial intended to assess the effect of vitamin D₃ supplementation on cardiometabolic risk markers (www.clinicaltrials.org: NCT00858247). Inclusion criteria were age between 12 and 18 years, BMI $\geq$ 95th percentile for age and sex, and euthyroid status as defined by normal TSH and fT4 levels. The reference range for TSH was 0.3–5.0 mIU/L, and for fT4 it was 0.8–1.8 ng/dL (20). Exclusion criteria included current cancer, hepatic or renal disorders, and use of metformin, oral hypoglycemic medications, or glucocorticoids in the previous six months. The protocol for the study was approved by Institutional Review Board of the Mayo Clinic. Informed consent and assent were obtained from participants and parents. The subjects' BMI z-scores were determined using the age- and sex-specific median BMI, generalized coefficient of variation (S), and the power of the Box-Cox transformation (L) based on U.S. Centers for Disease Control and Prevention growth curves (20).

Laboratory studies

Weight, height, and blood pressure measurements were made using standard protocols and equipment. After at least 12 h of fasting, blood samples were drawn, and all subjects underwent a 3 h oral glucose tolerance test (OGTT). After subjects received a 75 g oral glucose load, blood samples were obtained at 0, 10, 20, 30, 60, 90, 120, and 180 minutes for measurements of plasma glucose, C-peptide, and plasma insulin concentrations.

Plasma and serum samples were placed on ice, centrifuged at 4°C, separated, and stored at –80°C until assayed. Plasma glucose concentrations were measured using a glucose oxidase method (Yellow Springs Instruments); plasma insulin using a chemiluminescence assay (Access Assay; Beckman Coulter, Inc.). Serum concentrations of TSH and fT4 were measured using electrochemiluminescent immunoassays (TSH: Roche Diagnostics Corp.; fT4: Bayer Diagnostics). Total triiodothyronine (T3) was measured by electrochemiluminescence

Immunoassay (Roche Diagnostics). Serum total cholesterol, high-density lipoprotein cholesterol (HDL-C), and TG levels were measured by an enzymatic colorimetric assay (Roche Diagnostics). Non-HDL cholesterol was calculated as: Total cholesterol – HDL-C. The low-density lipoprotein cholesterol (LDL-C) was calculated as: Total cholesterol – HDL-C – TG/5.

Specific enzyme-linked immunosorbent assays (ELISA) were used to measure total- and high-molecular weight (HMW) adiponectin, retinol binding protein-4 (RBP4; ALPCO) and IL-6 (R&D Systems, Inc.).

Insulin sensitivity (S_i) was calculated from plasma glucose and insulin concentrations measured during the 3 h OGTT using the oral glucose minimal model approach (10,21–24). The S_i index measures the overall effect of insulin on stimulating glucose disposal and inhibiting glucose production. This index has been validated against the euglycemic clamp (22).

The β -cell responsivity indices were calculated from plasma glucose and C-peptide concentrations measured during the OGTT. The oral C-peptide minimal model incorporating age-associated changes in C-peptide kinetics was used, as measured by Van Cauter *et al.* (25). Calculation of the insulin secretion rate is essentially the calculation of the C-peptide secretion rate, as previously described utilizing standardized clearance rates for C-peptide (20). The model assumes that β -cell responsiveness (ϕ_{total}) is composed of two parts: a dynamic component (ϕ_d), which is proportionate to the rate of rise of glucose; and a static component (ϕ_s) that represents the response to the increment in glucose above the basal concentration (10,22,24).

The appropriateness of insulin secretion for the prevailing degree of S_i is assessed by calculating the total disposition index (DI_{total}), which expresses β -cell responsivity for the prevailing S_i ($\phi_{\text{total}} \times S_i$).

Statistical analyses

The distribution of each laboratory parameter was assessed graphically, and measurements that did not follow a normal distribution (fasting insulin, S_i , LDL-C, and TG) were transformed using the natural logarithmic transformation. Simple correlations were summarized using Pearson's correlation coefficient. The relationship between TSH, fT4, or total T3 and each of the laboratory parameters (dependent variables) was evaluated in a separate general linear model. Each model was assessed for two-way intersensitivity effects with sex, age, and BMI. In the absence of any statistically significant intersensitivity effects, the models were adjusted for these three factors. All calculated *p*-values were two-sided, and *p*-values < 0.05 were considered statistically significant. Analyses were performed using JMP v10.0 (SAS Institute Inc.).

Results

Baseline demographic and laboratory characteristics of the subjects are outlined in Table 1. The mean age of the subjects was 14.3 ± 1.88 years, and the mean BMI was 32.5 ± 4.65 kg/m². All subjects except one were non-Hispanic white, and 17 out of 36 subjects (47%) were male. None of the subjects in the study was prepubertal. Three males were in early puberty (one in Tanner stage 2 and two in Tanner stage 3), whereas one female was in early puberty (Tanner stage 3) (26,27). The mean TSH was 2.7 ± 1.2 mIU/L. Eleven out of 36 subjects

TABLE 1. BASELINE DEMOGRAPHIC, CLINICAL, AND BIOCHEMICAL CHARACTERISTICS OF STUDY PARTICIPANTS, AND COMPARISON BETWEEN MALES AND FEMALES^a

Baseline characteristics	Male (n = 17)	Female (n = 19)	p-Value (male vs. female)	Total cohort (n = 36)
Age (years)	14 (1.84)	14.6 (1.92)	0.32	14.3 (1.88)
Ethnicity (% white) ^b	100	94.7	0.25	97.2
BMI	31.4 (5.28)	33.6 (3.65)	0.15	32.5 (4.57)
BMI z-score	2.15 (0.07)	2.1 (0.07)	0.72	2.13 (0.3)
TSH (mIU/L)	2.39 (0.87)	3.05 (1.38)	0.09	2.74 (1.20)
ftT4 (ng/dL)	1.08 (0.18)	1.12 (0.12)	0.45	1.10 (0.15)
Insulin sensitivity (10 ⁻⁴ dL/kg/min per μ U/mL)	9.44 (6.59)	8.03 (6.18)	0.51	8.69 (6.32)
Disposition Index (10 ⁻¹⁴ dL/kg/min pmol/L)	1655.4 (1325.4)	1079.4 (726.8)	0.11	1342.7 (1067.4)
Total adiponectin (μ g/mL)	12.95 (6.18)	13.67 (6.30)	0.73	13.3 (6.16)
HMW adiponectin (μ g/mL)	8.02 (5.31)	8.01 (5.38)	0.99	8.01 (5.27)
IL-6 (pg/mL)	1.65 (0.99)	2.2 (0.98)	0.10	1.94 (1.0)
RBP4 (mg/mL)	31.3 (10.4)	26.7 (10.6)	0.20	28.86 (10.62)
Total T3 (ng/dl)	155.94 (23.89)	140.53 (18.67)	0.037	147.8 (22.39)

^aData are presented as mean (standard deviation) unless otherwise indicated.

^bChi-square test.

BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); ftT4, free thyroxine; HMW, high molecular weight; IL-6, interleukin-6; RBP4, retinol binding protein-4; TSH, thyrotropin.

had an impaired fasting glucose (range 101–114 mg/dL; reference range 70–100 mg/dL), and four subjects had an elevated fasting insulin (range 32.8–81.6 μ IU/mL; reference range 2.6–24.9 μ IU/mL). Males and females did not differ at baseline in terms of mean age, BMI, BMI z-score, TSH, ftT4, total and HMW adiponectin, IL-6, S_i, and disposition index (DI). Total T3 was higher in males compared to females ($p=0.037$).

Thyroid function tests and BMI

In the overall sample, TSH was not correlated with BMI (Spearman coefficient 0.27, $p=0.11$). There was a significant association between TSH and BMI in females (Spearman coefficient 0.53, $p=0.03$) but not in males (Spearman coefficient -0.01 , $p=0.96$). However, this association of TSH with BMI in females did not persist after adjustment for age in a multivariate regression model ($p=0.17$). There was no association between TSH and BMI z-scores (Spearman coefficient 0.14, $p=0.42$).

Thyroid function tests and insulin sensitivity

There was a statistically significant negative correlation between TSH and S_i in the entire cohort ($p=0.03$; Table 2). This negative correlation between TSH and S_i remained significant after adjustment for BMI ($p=0.024$) and age ($p=0.03$); and when assessed by sex, increasing concentrations of TSH were correlated with decreasing S_i in males (log S_i; Spearman coefficient -0.58 , $p=0.02$) but not in females (Fig. 1A and B). There was also no correlation between TSH and TG/HDL index ($p=0.76$) in the entire group and within the females and males separately. There was no correlation between TSH and DI ($p=0.48$) in either sex. There was a positive association between TSH and fasting glucose in females after adjustment for BMI, age, and fasting insulin ($p=0.04$), but TSH was not associated with fasting insulin (log transformed) on linear or multivariate linear regression models. ftT4 was not significantly associated with S_i before or after adjustment for BMI and age. Stratification by sex also did not reveal an association of ftT4 with insulin sensitivity

TABLE 2. UNADJUSTED CORRELATIONS OF THYROID FUNCTION TESTS WITH S_i AND DI

	Entire cohort (N = 36) correlation coefficient (p-value)	Male (n = 17) correlation coefficient (p-value)	Female (n = 19) correlation coefficient (p-value)
TSH			
S _i (10 ⁻⁴ dL/kg/min per μ U/mL)*	-0.09 (0.03)	-0.56 (0.02)	0.02 (0.92)
DI (10 ⁻¹⁴ dL/kg/min per pmol/L)	-0.13 (0.47)	-0.44 (0.08)	0.13 (0.60)
Fasting glucose (mg/dL)	0.08 (0.63)	-0.33 (0.12)	0.34 (0.15)
Fasting insulin* (μ IU/mL)	0.13 (0.45)	0.07 (0.78)	0.11 (0.66)
ftT4			
S _i (10 ⁻⁴ dL/kg/min per μ U/mL)*	0.02 (0.91)	0.11 (0.68)	0.08 (0.74)
DI (10 ⁻¹⁴ dL/kg/min per pmol/L)	0.05 (0.76)	0.19 (0.47)	0.007 (0.98)
Fasting glucose (mg/dL)	-0.30 (0.08)	-0.24 (0.35)	-0.40 (0.08)
Fasting insulin* (μ IU/mL)	0.18 (0.30)	0.21 (0.42)	0.13 (0.60)

Text in bold represents statistically significant correlations ($p<0.05$).

*Fasting insulin and S_i were log transformed.

DI, disposition index; S_i, insulin sensitivity.

FIG. 1. Correlation of thyrotropin (TSH; mIU/L) with insulin sensitivity (S_i) 10^{-4} dL/kg/min $\cdot$ per μ U/mL in (A) females and (B) males.

($p > 0.12$). fT4 was not associated with either fasting glucose or fasting insulin. Total T3 was also not associated with insulin sensitivity ($p = 0.58$) or DI ($p = 0.7$).

Thyroid function tests and lipids

Serum TSH correlated with LDL-C (Spearman coefficient 0.34, $p = 0.04$). In multivariable linear regression, this relationship did not remain significant after adjustment for BMI ($p = 0.44$), age ($p = 0.61$), and S_i ($p = 0.20$). Neither TSH nor fT4 correlated with HDL-C, total cholesterol, or TG before or after adjustment for age, BMI, or sex ($p > 0.05$).

Thyroid function tests and adipokines

Serum TSH correlated with IL-6 (Spearman coefficient 0.36, $p = 0.03$; Table 3). In multivariable linear regression, this relationship was attenuated slightly after adjustment for BMI ($p = 0.07$) and age ($p = 0.08$). fT4 was not associated with IL-6. fT4 and TSH were not associated with total or HMW adiponectin or RBP4 before or after adjustment for age, BMI, or sex ($p > 0.10$).

Discussion

This study suggests that TSH levels in euthyroid, non-diabetic, obese adolescent males are negatively associated with insulin sensitivity, determined using the oral minimal model approach. The sex-specific differential negative association of TSH with insulin sensitivity, even after controlling for BMI, is a somewhat surprising but novel finding.

No association was found between TSH and pancreatic β -cell function, lipids, and the adipokines measured.

The finding of a negative association between TSH and insulin sensitivity in obese adolescents is consistent with previous reports, using surrogate markers for insulin resistance derived from fasting glucose and insulin (7,28). To the authors' knowledge, this is the first study to examine the relationship between TSH and S_i in adolescents using a dynamic test for S_i . The sex-specific differences noted in our study are likely secondary to sex being an important covariate in determining insulin action (29). Additionally, these differences may be related to difference in timing of onset of puberty, with pubertal development occurring earlier in females than in males (mean age of onset of puberty being 10.5 years in females and 11.5 years in males) (30). None of the subjects in the study was prepubertal. Three males were in early puberty (one in Tanner stage 2 and two in Tanner stage 3), whereas one female was in early puberty (Tanner stage 3). The remainder of the subjects was in Tanner stage 4 or 5. Despite the majority of subjects in both groups being pubertal and the mean age being similar between males and females (14 years in males and 14.6 years in females), the sex steroid profiles were likely more mature and closer to adulthood in females than in males. The positive correlation between TSH and fasting glucose in females that persisted after adjustment for BMI and age also suggests that there might be an association between thyroid function and insulin sensitivity in females.

In the current study, the negative association in boys between TSH and S_i , measured using the oral glucose minimal

TABLE 3. UNADJUSTED CORRELATIONS OF TSH (mIU/L) AND fT4 (ng/dL) WITH LIPIDS AND ADIPOKINES LDL AND TG WERE LOG TRANSFORMED

	Entire cohort (N=36) correlation coefficient (p-value)	Male (n=17) correlation coefficient (p-value)	Female (n=19) correlation coefficient (p-value)
<i>TSH</i>			
Total cholesterol (mg/dL)	0.30 (0.06)	0.16 (0.52)	0.43 (0.06)
LDL cholesterol (mg/dL)	0.33 (0.04)	0.34 (0.18)	0.31 (0.19)
HDL cholesterol (mg/dL)	0.18 (0.28)	0.19 (0.47)	0.05 (0.83)
Triglycerides (mg/dL)	0.04 (0.81)	-0.12 (0.65)	0.28 (0.25)
IL-6 (pg/mL)	0.36 (0.03)	0.13 (0.63)	0.32 (0.18)
Total adiponectin (μ g/mL)	0.22 (0.18)	0.32 (0.21)	0.07 (0.77)
HMW adiponectin (μ g/mL)	0.29 (0.08)	0.28 (0.27)	0.17 (0.50)
RBP-4 (mg/mL)	0.01 (0.94)	0.28 (0.25)	0.23 (0.38)
<i>fT4</i>			
Total cholesterol (mg/dL)	-0.08 (0.63)	-0.27 (0.30)	0.13 (0.61)
LDL cholesterol (mg/dL)	-0.20 (0.24)	-0.50 (0.05)	-0.03 (0.90)
HDL cholesterol (mg/dL)	-0.11 (0.52)	-0.2 (0.43)	-0.009 (0.97)
Triglycerides (mg/dL)	0.25 (0.13)	0.25 (0.33)	0.27 (0.27)
IL-6 (pg/mL)	0.18 (0.29)	0.40 (0.10)	-0.16 (0.50)
Total adiponectin (μ g/mL)	0.13 (0.46)	0.21 (0.40)	-0.10 (0.71)
HMW adiponectin (μ g/mL)	0.14 (0.41)	0.12 (0.63)	0.14 (0.57)
RBP-4 (mg/mL)	0.05 (0.76)	0.07 (0.77)	0.15 (0.54)

^aData are presented as mean (standard deviation) unless otherwise indicated.
HDL, high-density lipoprotein; LDL, low-density lipoprotein.

model, persisted even after adjusting for BMI, thereby suggesting that this association is not solely attributable to obesity (31–33). The relationship between TSH and S_i is likely related to the decreased transcription and or translocation of glucose transporter 4 (GLUT4) in insulin-sensitive tissues, such as skeletal muscle and adipose tissue, as previously suggested (34–37).

The correlation between IL-6 and TSH noted in the study population is likely related to the presence of low-grade inflammation that occurs in obese individuals (38). Elevated serum RBP4 levels are associated with reduced expression of GLUT4 in adipocytes, an early pathological feature of insulin resistance (39). Elevated serum RBP4 levels have been reported in obese and insulin-resistant adults (39) and children (40). Although a relationship between RBP4 and TSH was reported in the elderly population with subclinical hypothyroidism and normal glucose tolerance (41), such a relationship between TSH and RBP4 was not found in the current study. Similarly, although adiponectin levels are known to be positively associated with insulin sensitivity, no such association between TSH and adiponectin was found. The present finding of a lack of an association between TSH and/or fT4 and adiponectin is in agreement with that in adults showing lack of difference in adiponectin levels between hypothyroid or euthyroid adults (17,42,43).

The finding of a lack of an association between TSH and lipids after controlling for S_i and BMI is similar to that reported by Reinehr *et al.* (44). However, the finding of a lack of association between TSH and TG found in the current study is contrary to earlier reports (3,7,8). These differences may be related to the smaller sample size, diverse characteristics of the children (3,7,8), and the absence of patients with an elevated TSH. In fact, previous studies had several participants with elevated TSH levels. For example, in the study by Shalitin *et al.* (8), 22% of patients had an elevated

TSH (8). Recent studies in healthy adults and subjects with type 2 diabetes report intersensitivity of TSH with insulin sensitivity in their association with plasma lipids (45). The present study suggests that insulin sensitivity and LDL-C levels may be interrelated independently of TSH, and insulin sensitivity may contribute partially to the observed relationship between TSH and LDL-C.

A strength of the current study is the use of the oral glucose minimal model for assessment of insulin sensitivity, as opposed to other surrogate measures of insulin resistance such as insulin levels and HOMA-IR. The ethnic homogeneity of the study population and absence of autoimmune thyroiditis in the study population are other strengths. The limitations of the study include the relatively small sample size, the cross-sectional nature of the study design and lack of a non-obese control group. Although, BMI was adjusted for, other potential confounding variables such as genetic, dietary, and environmental factors related to S_i and dyslipidemia were not included in the analysis.

This study has important clinical implications, as TSH levels have been noted to be higher in obese children (usually between 4 and 10 mIU/L) compared with normal weight children, and these are associated with normal fT4 levels and normal or slightly elevated fT3 levels (46). Several mechanisms have been hypothesized for an elevation of TSH in obesity, including derangement in the hypothalamic–pituitary axis, impaired feedback due to a lowered number of T3 receptors in the hypothalamus (thyroid hormone resistance), a decrease in peripheral thyroid hormone deiodinase activity, and leptin-mediated production of pro-TRH (46). The consequences of an elevated TSH in obesity remain unclear, and weight loss in obese children has been shown to be associated with a decrease in TSH levels (47,48). While a causal relationship is difficult to ascertain, the finding of a negative association between TSH (within the normal reference range)

and S_i in obese male adolescents is intriguing, particularly due to the ongoing debate about the “optimal” cutoff for the reference range for TSH values (2,49).

In conclusion, the current study suggests that increasing concentrations of TSH, even within the normal range, in non-diabetic obese adolescent males are associated with the deterioration of insulin sensitivity. Whether these findings carry implications regarding the definition of “optimal” TSH levels in adolescents at increased risk for diabetes needs to be studied further. Prospective clinical trials are warranted to determine whether lowering TSH levels into the lower half of the traditional “reference” range in obese children being treated with levothyroxine is beneficial in improving insulin sensitivity and preventing development of type 2 diabetes.

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Author Disclosure Statement

The authors have no disclosures. No competing financial interests exist.

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Address correspondence to:
Seema Kumar, MD
Mayo Clinic
200 First Street SW
Rochester, MN 55905

E-mail: kumar.seema@mayo.edu