

The Prevalence of Elevated Serum Thyroid-Stimulating Hormone in Childhood/Adolescent Obesity and of Autoimmune Thyroid Diseases in a Subgroup

Samar K. Bhowmick, MD, FACE; Gayathri Dasari, MD; Kara L. Levens, RN, BSN, CDE; and Kenneth R. Rettig, MD

Objectives: 1) To ascertain the frequency of elevated thyroid-stimulating hormone (TSH) level in obese children and adolescents and 2) to determine the prevalence of positive thyroid antibodies in the subgroup of obese children with elevated serum TSH concentration.

Methods: Retrospective chart review and prospective observation of 308 children, ages 6–17 years, with nonorganic, nonsyndromic obesity with BMI >97th percentile. The control population consisted of 286 nonobese, otherwise-healthy children of the same age range. Thyroid function tests (free T₄ or T₄ with TSH) were obtained on all patients in both groups. Thyroid antibodies (thyroid peroxidase and thyroglobulin) were determined among those with elevated TSH levels.

Results: Elevated TSH levels of >4 uIU/ml (reference interval 0.4–4) were noted in 36 patients within the obese group (11.7%) but only two in the control group (<0.7%). Five out of the 36 in the obese subgroup with elevated TSH levels had positive thyroid antibodies (14%). All five subjects in the obese subgroup with positive thyroid antibodies had TSH levels >7.4 uIU/ml, with an average of 9.8 uIU/ml. Thirty-one children in the obese subgroup with negative thyroid antibodies had TSH levels <6.7 uIU/ml (average 5.33 uIU/ml).

Conclusion: A higher prevalence of TSH elevation was observed in the obese group (11.7%) than in the control group (0.7%). Positive thyroid peroxidase and thyroglobulin antibodies were observed in higher frequency in the obese subgroup with an elevated TSH level. The obese subgroup with positive thyroid antibodies also had higher TSH levels. Therefore, some instances of high TSH, especially those associated with antibodies, are likely due, at least in part, to thyroid disease, and others (possibly a majority) may be due to obesity, not its cause. It remains to be seen whether any children with mild TSH elevation benefit from thyroid hormone treatment.

Key words: obesity ■ body mass index ■ thyroid ■ children/adolescents

© 2007. From the Division of Endocrine and Metabolic Disease, University of South Alabama College of Medicine, Mobile, AL (Bhowmick, Rettig, professors of pediatric); Emory University, Atlanta, GA (Dasari, pediatric endocrinology fellow); and Department of Pediatrics, Division of Endocrine and Metabolic Disease, USA Hospital Systems (Levens). Send correspondence and reprint requests for *J Natl Med Assoc.* 2007;99:773–776 to: Dr. Samar K. Bhowmick, University of South Alabama College of Medicine, 2451 Fillingim St., Suite 212, Mobile, AL 36617-2293; phone: (251) 470-1662; fax: (251) 471-7722; e-mail: sbhowmick@usouthal.edu

INTRODUCTION

Obesity among children and adolescents is an increasing problem in the United States as well as in developing countries. Primary care physicians are now increasingly involved in the initial evaluation of these children. Hypothyroidism is often thought to be the cause of obesity, and thyroid function tests are the most commonly performed laboratory studies in this population even though massive obesity is rarely explained by hypothyroidism. Like others, we believe that many of these children are unnecessarily treated with thyroid hormone replacement simply on the basis of mild TSH elevation.^{1–3} Reports of mild TSH elevation in obese children were initially published from Germany.³ Another smaller series from Europe also reported higher prevalence of elevated serum TSH, T₄ and T₃ in obese children.⁴ Our series is larger than any published report. We submit our observation of the prevalence of TSH elevation in obese children and adolescents and the incidence of positive thyroid antibodies in those with elevated TSH, suggesting an autoimmune thyroid disorder. Possible mechanisms of TSH elevation, incidence of thyroid antibodies in obese children and limitation of our study are discussed in the text.

METHODS

This study was approved by the institutional review board (IRB) within our institution. We examined and reviewed thyroid function studies in 308 obese children (192 girls and 116 boys aged 6–17 years, average age

11.9 years) with nonorganic, nonsyndromic obesity. Obesity was defined by a body mass index (BMI) >97th percentile. BMI levels were calculated by weight (kg) divided by stature (cm²) multiplied by 10,000. One-hundred-seventy-seven patient charts were retrospectively reviewed, and 201 patients were prospectively observed and reviewed. The control group consisted of 286 children (197 boys and 89 girls in a similar age range). All of the children in the control group had a BMI <80th percentile without any evidence of endocrine disease. The majority of the children had a diagnosis of constitutional delay of growth, familial short stature, delayed puberty or were evaluated in pediatric clinic for other nonendocrine-related problems. Of the control group, 135 patient charts were retrospectively reviewed and 151 were prospective observation and review. To be included in this study, the patient had to have a serum total T₄ or free T₄ with TSH measurement and determination of thyroid antibodies [thyroid peroxidase (TPO-Ab) and thyroglobulin (TG-Ab)] if the TSH was elevated. Routine physical and thyroid examinations were performed on the obese group by one of two board-certified pediatric endocrinologists. Statistical analysis was performed by Subhash Aryal, PhD, Department of Biostatistics, University of Illinois at Chicago. The Fisher exact t test was used for statistical analysis and a P value <0.05 was considered statistically significant.

RESULTS

Elevated TSH levels of >4 uIU/ml were noted in 36 patients within the obese group (11.7%) but in only two in the control group (0.7%). Five out of the 36 in the obese subgroup (15%) with elevated TSH levels had positive thyroid peroxidase (TPO-Ab) and thyroglobulin (TG-Ab) antibodies. All five subjects in the obese subgroup with positive thyroid antibodies had TSH levels

>7.4 uIU/ml, with an average of 9.8 uIU/ml. Thirty-one children in the obese subgroup with negative thyroid antibodies had TSH levels <6.7 uIU/ml (average 5.33 uIU/ml), except for one individual who had a TSH level of 8.4 uIU/ml.

In the control group, only two children had elevated TSH levels. One had positive thyroid antibodies and a TSH level of 8.8 uIU/ml, and the other—with negative thyroid antibodies—had a TSH level of 4.4 uIU/ml (P value <0.001). The profiles of the obese, control and subgroups are in Tables 1 and 2.

DISCUSSION

The incidence of childhood obesity is rising within the United States and other developing countries. The relationship between obesity and thyroid dysfunction is a topic of great interest as a large number of these children are now seeking medical attention. Much of the rationale in trying to identify abnormalities of thyroid function in obesity is based on the concept that in hypothyroidism “slow metabolism leads to obesity.” This view is frequently shared by primary care physicians as well as by patient families. While abnormalities of other hypothalamic pituitary hormone axis have been described,^{1,2,5,6} studies of thyroid function in obesity reveal a variety of inconsistencies from normal thyroid function tests, to high serum T₃ levels and low to exaggerated TSH response to thyrotropin-releasing hormone (TRH).^{1,5,7-9}

Stichel et al.,³ in a large cohort of 290 obese children, found a higher prevalence of TSH elevation (7.5%) over the control group of (0.3%). The obese subgroup of 17 who had elevated TSH also had higher percentage of positive thyroid antibodies (25.5% for TPO-Ab and 17% for TG-Ab). Reinher and Andler, in a series of 119 obese children, found 12% had elevated TSH levels, 15% had elevated T₃ levels and 11% had T₄ concentration of <2

Table 1. Result: obese and control groups

OBESE				CONTROL		
	Age: 6–17 years (11.9)		Positive TA with ↑TSH	Age: 6–16 years (9.6)		Positive TA
	BMI: 26–60 kg/m² (37)	Elevated TSH		BMI: 12–23 kg/m² (16)	Elevated TSH	
Number:	308	36 (11.7%)	5 (14)%	286	2 (0.7%)	1
Sex:	M/F 116/192	14/22	1/4	197/89	1/1	F
TSH uIU/ml	0.43–14.1 (2.51)	4.2–14.1 (5.33)	7.4–14.1 (9.8)	0.3–8.8 (1.55)	4.4–8.8	8.8
T4 ug/dl	4.6–11.9 (8.7)	4.2–8.4 (5.33)	4.6–7.0 (5.8)	4.7–11 (7.2)	8.7	
	(4.5–11.5) N=181	N=21	N=2	N=183	N=1	N/P
FT4 ng/dl	0.79–1.5 (1.38)	0.9–1.7 (1.24)	0.79–1.3 (0.97)	0.79–1.7 (1.21)	0.81	0.81
	(0.8–1.9) N=127	N=15	N=3	N=103	N=1	

N: number on whom the test was performed, N/P: not performed, TA: thyroid antibodies; Reference range and average in parenthesis

standard deviation of normal-weight children.⁴ They also observed that weight reduction led to a long-term decrease in T₄ and T₃ levels but not in TSH levels.

We believe that our series is larger than any other published report and the first such North American study. It confirms the findings of elevated TSH in obese children and adolescents as observed by others. We found 11.5% of obese children in our series had elevated TSH and 14% of children with elevated TSH levels also had positive thyroid antibodies, suggesting an autoimmune thyroid disease. The obese subgroup of children with positive thyroid antibodies had higher individual and mean TSH levels than those with elevated TSH only. The mechanism of elevated TSH levels in obese children is unclear. Iodine deficiency does not appear to be a problem in our population. An increase in TSH levels could suggest a mild TSH resistant state similar to the insulin-resistant state observed in obesity.^{4,8} This theory has some merit, since T₃ receptors are decreased in obesity and the negative feedback between TSH and peripheral thyroid hormone is increased in obesity, resulting in a relative pituitary resistance to thyroid hormone.^{9,10} A TRH stimulation test (TRH-t) could be useful in determining whether pituitary response is altered in obese children.^{1,6} However, various studies showed inconsistency from normal to exaggerated response of TSH to TRH stimulation test in obese individuals.^{3,7,9} It is also postulated that the production of TSH is also regulated by transmitters and hormones that regulate body weight and satiation such as neuropeptide Y (alpha), melanocyte-stimulating hormones and the agouti-related peptide innervating TRH-synthesizing neurons.^{3,11} These transmitters are also influenced by leptin, which correlates with the degree of obesity. Some studies have described a correlation between leptin and TSH. Leptin has also been described as a mediator responsible for the increased production of TSH.¹²⁻¹⁵ In other studies, no significant correlation between TSH and leptin level has been noted.^{4,16} Factors such as timing of blood sampling may influence TSH concentration.^{17,18} However, this does not explain the elevation of TSH in our obese group since blood samples were drawn at random in the control group as well. The high prevalence of elevated thyroid antibody

titers in the obese population has been observed by Lima et al. In a large series among 1,987 adult obese patients from the Pima Indian tribe in Brazil, 15.8% had positive thyroid antibodies.¹⁹ It has been postulated that a high incidence of thyroid antibodies in obese individuals may be a result of increased antigens presented by amplified thyroid stimulation.³ The significance of thyroid autoimmunity in obesity is of some concern and interest since these individuals are at high risk of developing symptomatic hypothyroidism, which may contribute further to weight gain or may prevent weight loss.

There are several limitations in our study: we did not measure T₃ or free T₃ in many of these patients and as a result cannot comment on the observation of elevated T₃ in obese individuals that has been reported in other studies.^{1,4,5} We also did not measure the leptin level in the obese group. Follow-up thyroid function test was difficult because of lack of weight loss in the majority of our patients as well as noncompliance with clinic visits. It would have been ideal to have performed thyroid antibodies on all subjects in the obese and control groups in order to determine the prevalence of positive thyroid antibodies, even in those children who did not have TSH elevation. A TRH-t to assess the TSH response would have been interesting, but the product was not available to us. Although clinical examinations were done by experienced pediatric endocrinologists, thyroid sonograms were not done on most of our patients in the obese group to assess thyroid volume and size, specifically those with elevated TSH levels since enlarged thyroid volume related to increased BMI and elevated TSH levels have been reported.^{20,21}

In conclusion, there are varieties of tantalizing possible abnormalities of hypothalamic pituitary thyroid function in obesity, but they do not seem to fit in a coherent whole. It is not clear from various studies that mild TSH elevation is frequently observed in children and adolescents who are obese. Thyroid antibodies should be checked in all individuals with elevated levels of TSH to ensure that there is no underlying autoimmune thyroid disorder. An elevated TSH with positive thyroid antibodies may suggest compensated hypothyroidism and may require treatment to prevent further weight gain. Howev-

Table 2. Subgroups: elevated TSH with positive TA obese group

Age (Years)	Sex	BMI	T ₄ (4.5–1.5) ug/dl	F T ₄ (0.8–1.9) ng/dl	TSH (0.4–4.0) uIU/ml	TPO-Ab (<35) IU/ml	TG-Ab (<40) IU/ml
12	M	35.6	N/P	1.3	9.3	>1,000	90
16	F	33.5	N/P	0.82	14.1	>1,000	664
11	F	38	N/P	0.79	9.17	400	97
13	F	31	4.6	N/P	7.4	286	304
16	F	47	7.0	N/P	8.9	>1,000	70
<i>Control Group</i>							
12	F	21	N/P	0.8	8.8	>1,000	340

er, patients must be counseled that thyroid hormone replacement alone is not going to help them to lose weight until they follow a prudent nutritional plan and exercise program. Mild TSH elevation alone, with negative thyroid antibodies, in our opinion, does not require thyroid hormone replacement but may require observation. Physicians caring for children and adolescents with obesity should be aware of these findings so as not to mislead their patient and family in thinking that thyroid dysfunction is the cause of obesity.

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