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BRIEF REPORT

Hyperthyrotropinemia in Obese Children Is Reversible after Weight Loss and Is Not Related to Lipids

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Context: There is some controversy whether T_4 treatment is indicated in obese humans with hyperthyrotropinemia.

Objective: The objective of this study was to examine whether hyperthyrotropinemia is a cause or a consequence of obesity.

Design: The study was designed as a cross-sectional comparison between obese and lean children and includes a 1-yr follow-up study.

Setting: The study was set in a primary care facility.

Patients: The patients were 246 obese and 71 lean children.

Intervention: The 1-yr intervention program was based on exercise, behavior therapy, and nutrition education.

Main Outcome Measures: The main outcome measures were TSH, free T_3 (fT3), free T_4 (fT4), high-density lipoprotein, low-density lipoprotein, and total cholesterol at baseline and 1 yr later.

Results: TSH ($P = 0.009$) and fT3 ($P = 0.003$) concentrations were significantly higher in obese children than in normal weight children, whereas there was no difference in fT4 levels ($P = 0.804$). Lipids did not correlate significantly to thyroid hormones in cross-sectional and longitudinal analyses. fT3, fT4, and lipids did not differ significantly in the 43 (17%) children with TSH levels above the normal range from the children with TSH levels within the normal range. Substantial weight loss in 49 obese children led to a significant reduction of TSH ($P = 0.035$) and fT3 ($P = 0.036$). The 197 obese children without substantial weight loss demonstrated no significant changes of thyroid hormones.

Conclusions: Because fT3 and TSH were moderately increased in obese children and weight loss led to a reduction, the elevation of these hormones seems to be rather a consequence of obesity than a cause of obesity. Because fT3 and TSH were both increased in obesity and thyroid hormones were not associated to lipids, we put forward the hypothesis that there is no necessity for thyroxine treatment. (***J Clin Endocrinol Metab* 91: 3088–3091, 2006**)

IN RECENT YEARS, there has been an increasing focus on thyroid function in obesity. Some studies have reported moderately elevated TSH levels in obese subjects (1, 2). This condition is supposed to be associated with weight gain, dyslipidemia, ischemic heart disease, and all-cause mortality, but the findings are inconsistent (2, 3). Furthermore, there still is considerable disagreement regarding whether and when to start treatment (4, 5).

To clarify this question, it would be interesting to determine whether hyperthyrotropinemia in obesity is related to lipids and whether the changes of thyroid hormones are a cause or a consequence of being overweight. The aim of this study was to analyze whether the changes of TSH and the free amount of peripheral thyroid hormones in obesity are reversible and/or related to lipids. We studied the changes of thyroid hormones [free T_3 (fT3), free T_4 (fT4), and TSH] and the changes of lipids in obese children participating in a 1-yr outpatient obesity intervention. Additionally, a TRH test was performed in a subgroup of obese children with hyperthyrotropinemia to detect altered pituitary responsiveness.

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Abbreviations: BMI, Body mass index; E, energy intake; fT3, free T_3; fT4, free T_4; HDL, high-density lipoprotein; HOMA, homeostasis model assessment; IQR, interquartile range; LDL, low-density lipoprotein; SDS, SD score.

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Subjects and Methods

We examined 246 obese children attending the obesity intervention program "Obeldicks" and 71 nonobese children of the same age, pubertal stage, and gender distribution. Children with endocrine or metabolic disorders were excluded from the study. Smokers and children taking any medication including oral contraceptives were also excluded.

Obesity was defined according to the body mass index (BMI) 97th percentile using the definition of the International Task Force of Obesity in Childhood (6). The weight status was calculated as SD score (SDS)-BMI using population-specific data and Cole's least mean square method, which normalizes the BMI skewed distribution (6, 7).

Thyroid hormones (TSH, fT3, and fT4) were determined in the fasting status in the nonobese children and in the obese children before and after participating in the 1-yr intervention. Fasting serum insulin, glucose, total cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol concentrations were analyzed in the obese children before and after the 1-yr intervention. TSH, fT3, and fT4 were determined by high-specific solid-phase technique-chemiluminescence-immunoassays (Immulite DPC, Los Angeles, CA). Intra- and interassay variations were less than 10%. Insulin, glucose, HDL and LDL cholesterol, and total cholesterol concentrations were measured using commercially available test kits (Total-C, LDL-C-, and HDL-C-Plus, Roche Diagnostics, Mannheim, Germany; Vitros analyzer, Ortho Clinical Diagnostics, Neckargemuend, Germany; MEIA, Abbott, Wiesbaden, Germany). Intra- and interassay variations were less than 5%. Homeostasis model assessment (HOMA) was used to detect the degree of insulin resistance (HOMA = [insulin (milliunits per liter) × glucose (millimoles per liter)]/22.5) (8).

In all children with a goiter or TSH levels more than 5 mU/liter, autoimmune thyroiditis was excluded by measuring antithyroidal peroxidase and thyreoglobulin antibodies. A TRH test [100 $\mu g/m^2$ body-surface TRH iv (Relefact TRH 200)] was performed with measurements of TSH at 0, 20, and 45 min in a subgroup of five randomly chosen obese children with TSH levels more than 5 mIU/liter.

The reduction of weight was achieved through the 1-yr obesity intervention program Obeldicks, which has been described in detail elsewhere (9, 10). Briefly, this program was based on physical exercise, nutrition education, and behavior therapy including the individual psychological care of the child and his/her family. The exercise therapy consisted of sports, instructions in physical exercise as part of everyday life, and in reduction of the amount of time spent watching television. The nutritional course was based on the prevention concept of the "optimized mixed diet", which was both fat and sugar reduced containing 30% energy intake (E) fat, 15 E% proteins, and 55 E% carbohydrates including 5 E% sugar (10). Substantial weight loss during the 1-yr intervention was defined by a decrease in SDS-BMI equal to or greater than 0.5, because, with a reduction of less than 0.5 SDS-BMI, no improvement of insulin resistance and cardiovascular risk factors could be measured in obese children (11).

Statistical analysis was performed using Winstat for Excel. Statistically significant differences were tested by Mann-Whitney *U* test for unpaired observations and by Wilcoxon test for paired observations. The obese children with TSH levels more than 97.5th percentile, which was calculated by the values of the normal weight children, were compared with the obese children with TSH concentrations less than or equal to 97.5th percentile with respect to peripheral hormones and lipids. Multiple linear regression analyses with lipids as dependent variables and age, gender, degree of overweight (BMI), pubertal stage, insulin resistance index (HOMA), and thyroid hormones as independent variables were performed. Gender and pubertal stage were used as classified variables. A $P < 0.05$ was considered statistically significant. The local ethics committee of the University of Witten/Herdecke approved this study. Informed consent was obtained from all subjects and their parents.

Results

The 246 obese children demonstrated significantly higher concentrations of TSH [median 2.4 (interquartile range, IQR, 1.8–3.2) mIU/liter, $P = 0.009$] and fT3 [median 4.2 (IQR 3.8–4.7) pg/ml, $P = 0.003$] compared with the 71 nonobese children [median TSH 2.2 (IQR 1.6–2.7) mIU/liter, median fT3 3.9 (IQR 3.5–4.4) pg/ml], whereas fT4 concentrations did not differ significantly [median 1.2 (IQR 1.1–1.4) ng/dl *vs.* median 1.2 (IQR 1.1–1.3) ng/dl, $P = 0.804$]. The obese children did not differ significantly in respect of age [median 10.4 (IQR 8.5–12.0) yr *vs.* median 11.1 (IQR 8.7–12.9) yr, $P = 0.332$], sex (55 *vs.* 58% girls, $P = 0.713$), and pubertal stage (55 *vs.* 49% prepubertal, $P = 0.197$) from the nonobese children. No child had a goiter, thyroidal autoantibodies, or clinical signs of hyperthyroidism or hypothyroidism.

In the multiple regression analyses adjusted for age, gender, pubertal stage, degree of overweight, and insulin resistance index (HOMA) of the 246 obese children, there were no significant correlations between TSH and HDL ($P = 0.199$), LDL ($P = 0.298$), and total cholesterol ($P = 0.939$), between fT3 and HDL ($P = 0.183$), LDL ($P = 0.935$), and total cholesterol ($P = 0.722$), as well as between fT4 and HDL ($P = 0.199$), LDL ($P = 0.088$), and total cholesterol ($P = 0.394$).

Forty-three obese children (17%) demonstrated TSH concentrations more than 97.5th percentile (TSH > 3.55 mU/liter). The fT3 and fT4 concentrations of these children were within the normal range (n = 38) or more than 97.5th percentile (fT3 > 5.3 pg/ml; n = 5). The children with TSH concentrations more than 3.55 mIU/liter did not differ significantly in their fT3, fT4, and lipid concentrations, or in age, gender, and degree of overweight from the children with TSH levels less than or equal to 3.55 mIU/liter (see Table 1).

In the TRH test, all five children responded with an increase of their baseline TSH levels (mean 5.7 mIU/liter) at 20 min (mean TSH 16.7 mIU/liter) and with a decrease at 45 min (mean TSH 12.7 mIU/liter).

Forty-nine obese children completed the intervention, Obeldicks, with substantial weight loss. These children did not differ significantly from the 197 children without substantial weight loss in respect of age ($P = 0.256$), gender ($P = 0.540$), degree of overweight (SDS-BMI, $P = 0.502$), thyroid hormones (TSH, $P = 0.081$; fT3, $P = 0.386$; fT4, $P = 0.156$), or lipids (LDL cholesterol, $P = 0.248$; HDL cholesterol, $P = 0.445$; total cholesterol, $P = 0.614$) at baseline. Compared with their initial levels, the children with substantial weight loss demonstrated a significant decrease of fT3 and TSH, and an improvement of lipids and insulin resistance index (HOMA), whereas there was no difference in fT4 concentrations (see Table 2). The thyroid hormones and HDL cholesterol concentrations of the 197 children without substantial weight loss did not significantly change in comparison to their initial values, whereas insulin resistance index (HOMA) significantly increased and total and LDL cholesterol significantly decreased, but in a lower degree than in the children with substantial weight loss (see Table 2).

In the 246 obese children, the changes of thyroid hormones

TABLE 1. Age, gender, degree of overweight (BMI, SDS-BMI), TSH, fT3, and fT4 serum levels in the obese children with TSH levels more than 97.5th percentile of the nonobese children compared to the obese children with TSH levels less than or equal to 97.5th percentile (data as median and IQR)

	TSH > 3.55 mIU/liter	TSH ≥ 3.55 mIU/liter	*P* value
n	43	203	
Gender	59% girls	55% girls	0.679
Pubertal stage	62% prepubertal	54% prepubertal	0.204
Age (yr)	9.5 (8.5–11.3)	10.9 (8.6–12.0)	0.101
BMI (kg/m^2)	26.6 (24.5–28.2)	27.4 (25.6–28.9)	0.150
SDS-BMI	2.4 (2.1–2.6)	2.4 (2.2–2.7)	0.486
TSH (mIU/liter)	4.3 (3.8–5.1)	2.1 (1.6–2.8)	<0.001
fT3 (pg/ml)	4.2 (3.8–4.9)	4.3 (3.8–4.7)	0.720
fT4 (ng/dl)	1.2 (1.0–1.3)	1.2 (1.1–1.4)	0.304
Total cholesterol (mg/dl)	177 (152–195)	170 (152–190)	0.100
LDL cholesterol (mg/dl)	114 (90–139)	110 (92–132)	0.599
HDL cholesterol (mg/dl)	45 (39–51)	46 (41–53)	0.488

TABLE 2. Degree of overweight (SDS-BMI), thyroid hormones, and lipids in obese children with and without substantial weight loss (data as median and IQR)

	Substantial weight loss			No substantial weight loss		
n	49			197		
Age	9.9 (7.9–11.9)			10.4 (8.8–12.0)		
Gender	59% girls			54% girls		
Pubertal stage	59% prepubertal			54% prepubertal		
	Baseline	1 yr later	*P* value	Baseline	1 yr later	*P* value
SDS-BMI	2.4 (2.2–2.8)	1.7 (1.3–1.9)	<0.001	2.4 (2.2–2.7)	2.3 (2.0–2.6)	<0.001
TSH (mIU/liter)	2.6 (1.6–3.3)	2.1 (1.5–2.7)	0.035	2.4 (1.8–3.2)	2.5 (1.8–3.5)	0.109
TSH > 3.55 mIU/liter	10 (20%)	4 (8%)		32 (16%)	42 (21%)	
fT3 (pg/ml)	4.3 (3.8–4.9)	4.1 (3.8–4.5)	0.036	4.2 (3.7–4.7)	4.2 (3.9–4.8)	0.242
fT4 (ng/dl)	1.2 (1.1–1.3)	1.3 (1.1–1.4)	0.249	1.2 (1.1–1.4)	1.2 (1.1–1.3)	0.081
Total cholesterol (mg/dl)	175 (153–188)	158 (140–178)	0.046	173 (152–194)	170 (150–192)	0.031
LDL cholesterol (mg/dl)	109 (92–132)	94 (79–119)	0.017	112 (92–133)	102 (83–127)	<0.001
HDL cholesterol (mg/dl)	45 (40–53)	47 (41–58)	0.021	46 (41–53)	47 (41–55)	0.162
Insulin resistance index (HOMA)	2.5 (1.8–3.8)	1.9 (1.1–3.2)	0.038	3.3 (2.4–4.5)	3.8 (2.5–5.1)	0.001

did not significantly correlate to the changes of total cholesterol (TSH, r = 0.08, $P = 0.112$; fT3, r = 0.03, $P = 0.309$; fT4, r = −0.01, $P = 0.444$), LDL cholesterol (TSH, r = −0.07, $P = 0.134$; fT3, r = 0.02, $P = 0.351$; fT4, r = 0.03, $P = 0.339$), and HDL cholesterol (fT3, r = 0.04, $P = 0.265$; fT4, r = −0.07, $P = 0.147$) calculated by partial correlation adjusted for changes in SDS-BMI apart from a very weak positive correlation between HDL cholesterol and TSH (r = 0.16, $P = 0.008$).

Discussion

Obese children demonstrated moderately increased serum levels of TSH and fT3 compared with children of normal weight, whereas there was no difference in fT4 concentrations. These findings are in concordance with other studies in children (12, 13) and adults (1, 2). A TRH test ruled out an alteration of pituitary responsiveness in obese children with elevated TSH levels. This finding, the normal fT4 concentrations, and the absence of clinical signs of hypothyroidism and hyperthyroidism speak against hormone resistance. In contrast to previous smaller studies in children with lower degrees of weight loss (12, 14), TSH and fT3 normalized after substantial weight loss in concordance with some studies in obese adults (15, 16) suggesting a reversible increase of these hormones in obesity.

The thyroid hormones demonstrated no significant relationship to lipids both in cross-sectional and longitudinal analyses. Furthermore, the lipids of the children with the highest TSH levels did not differ from the other children. Because TSH and the biologically active fT3 are both increased in obesity, and children with moderately elevated TSH levels demonstrated fT3 or fT4 levels in the normal upper range, we put forward the hypothesis that there is no necessity to treat hyperthyrotropinemia in obesity. However, peripheral thyroid hormones and thyroidal autoantibodies have to be determined in obese children with hyperthyrotropinemia to identify subclinical hypothyroidism based on autoimmune thyroiditis, which has to be treated.

The cause of the elevated TSH and fT3 levels in obesity remains unclear. In a pediatric study, the increase of TSH serum levels was not accounted for by iodine deficiency or autoimmune thyroiditis (13). Among others, the synthesis of TSH is also regulated by leptin, which regulates body weight and satiation, and innervates hypophysiotropic TRH neurons (17). Furthermore, there is a synchronicity between the secretion of leptin and TSH (18). The differences in 24-h TSH release correlated positively with the decline of circulating leptin in weight loss (15). Conversely, some studies have demonstrated no correlation between TSH and leptin (19).

Because thyroid hormones, especially T_3, regulate both the resting metabolic rate and thermogenesis and lead to lipolysis, changes of thyroid hormones could reflect an adaptation process in obesity. In concordance, thyroid volume decreased in weight loss (16). The reduction of fT3 concentrations after weight loss is associated with a reduction of resting metabolic rate and consequently a reduction in energy expenditure (12, 14). This condition may represent a cause of the difficulties to maintain weight loss.

This study has a few potential limitations. First, BMI percentiles were used to classify overweight. Although BMI is a good measure for overweight, one needs to be aware of its limitations as an indirect measurement of adiposity. Second, we evaluated changes of BMI in relation to thyroid hormones, whereas it might have been more appropriate to evaluate, or at least include, measurements of the lean body mass. Lean body mass appears to be a major determinant of thyroxine requirement (20).

In summary, moderately increased TSH and fT3 concentrations were frequently found in obese children. Substantial weight loss induced a normalization of these alterations. Because TSH and fT3 were both reversibly increased in obesity and were not related to lipids, we put forward the hypothesis that there is no necessity to treat the moderately elevated TSH levels in obese children.

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