Subclinical Hypothyroidism in Obese Patients: Relation to Resting Energy Expenditure, Serum Leptin, Body Composition, and Lipid Profile

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Abstract

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Objective: To evaluate whether subclinical hypothyroidism (SH) affects resting energy expenditure (REE) as well as body composition, lipid profile, and serum leptin in obese patients.

Research Methods and Procedures: A total of 108 obese patients with SH defined as normal free thyroxine levels and thyroid-stimulating hormone (TSH) values of >4.38 μU/ml (mean $\pm$ 2 SD of the values of our reference group of obese patients with normal thyroid function) were compared with a group of 131 obese patients matched for age, sex, and body mass index (BMI) but with normal TSH levels. We assessed estimated daily caloric intake by 7-day recall, REE by indirect calorimetry, body composition by bioelectrical impedance analysis, serum leptin by radioimmunoassay, and lipid profile (i.e., total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides).

Results: All of the variables measured were not different between the euthyroid obese patients and those with SH. In a multiple regression model with REE expressed for kilograms of fat free mass (REE/kgFFM) as a dependent variable and percentage of fat mass, BMI, waist-to-hip ratio, age, TSH, free thyroxine, serum leptin, and caloric intake as independent variables, only percentage of fat mass was significantly correlated with REE/kgFFM in both groups. In the SH group only, BMI, waist-to-hip ratio, age, and TSH were related to REE/kgFFM and explained 69.5% of its variability. After dividing the patients with SH using a cutoff TSH value of 5.7 μU/ml, which represents 3 SD above the mean of TSH levels of the group of obese patients with normal thyroid function, only REE/kgFFM was significantly different and lower in the group of more severely hypothyroid patients.

Discussion: In patients with obesity, SH affects energy expenditure only when TSH is clearly above the normal range; it does not change body composition and lipid profile. We suggest that, at least in obese patients, evaluation of TSH levels may be useful to rule out a possible impairment of resting energy expenditure due to a reduced peripheral effect of thyroid hormones.

Key words: thyroid function, risk factors, energy expenditure, fat-free mass, body mass index

Introduction

Whether a deficit in resting energy expenditure (REE) plays a role in the development of weight gain leading to obesity is matter of debate (1), but thyroid function, which affects energy expenditure, is generally normal in obesity.

The recent discovery of leptin, a peptidic hormone produced by adipose tissue, has led to a renewed interest in the pathophysiology of obesity; some studies have focused on the relationship between leptin and energy expenditure as well as thyroid function. Leptin physiologically increases energy expenditure (2), but in obesity the situation is less clear due to the condition of leptin resistance of most obese patients (3). As far as thyroid

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function is concerned, hypothyroid patients have been reported to have higher levels of leptin than healthy subjects matched for body mass index (BMI) (4), but other studies have not confirmed this finding (5–7). A single study has reported higher leptin levels in obese hypothyroid subjects than in obese euthyroid subjects (8).

Subclinical hypothyroidism (SH) is a common condition characterized by supranormal thyroid-stimulating hormone (TSH) levels, suggesting a mild impairment of a thyroid hormone effect at the tissue level, despite free thyroxine (FT_4) levels in the normal range. The aim of this work was to study a series of obese patients with or without SH to evaluate whether SH has any combined effect on energy expenditure, body composition, lipid profile, and leptin levels.

Research Methods and Procedures

Patients

The study included 108 obese patients referred to the Department of Endocrinology and Metabolic diseases of San Giuseppe Hospital, Istituto Auxologico Italiano, who had a mean ± SD BMI of 42.6 ± 6.6 kg/m^2 (range, 30.1 to 64.2 kg/m^2) and a TSH level of >4.38 μU/ml (see below for definition) but normal FT_4 levels, which allowed the diagnosis of SH. The failure of thyroid function was due to a partial thyroidectomy for nodular goiter in 18 patients and to autoimmune thyroiditis, diagnosed by positive antiperoxidase antibodies and the typical ultrasound picture, in the remaining patients. The cutoff limit of TSH corresponds to the mean ± 2 SD of the TSH concentration (1.96 ± 1.21 μU/ml) in a series of 114 obese patients with normal thyroid function (NTF), assessed by careful clinical and laboratory estimation (i.e., no history of thyroid diseases, normal FT_4 and FT_3 values, absence of antithyroid antibodies and TSH receptor antibodies, and normal ultrasound picture). A group of 131 obese patients that matched for age, sex, and BMI, but who had normal TSH levels (i.e., within 2 SD of the mean of our euthyroid obese series) were used as a control group. Patients who had concomitant, severe renal, hepatic, or cardiac disease, or who were being treated with drugs such as beta blockers, which could affect the variables of the study and in particular energy expenditure, were excluded; patients with fluid overload according to vectorial analysis (9,10) were also excluded to minimize errors of the bioelectrical impedance analysis (BIA) in estimating fat mass (FM) and fat-free mass (FFM) in severe obesity. The study was approved by the Hospital Ethics Committee; the aim and the design of the study were explained to the patients who gave their written informed consent.

All of the patients had stable weight during the month before the study. The study protocol included height, abdominal girth, and weight measurement for determination of BMI and waist-to-hip ratio (WHR), REE by indirect calorimetry, and body composition by BIA. Laboratory investigation included total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, uric acid, blood glucose, insulin, and serum leptin determined on a blood sample taken in the morning after an overnight fasting.

Table 1. Clinical, biochemical, and metabolic parameters (mean ± SD) in obese patients with SH and with normal thyroid function

Parameters	SH	Controls
Patients (no.)	108	131
Sex (males/females)	16/92	31/100
Age (years)	46.8 ± 15.7	47.8 ± 14.0
BMI (kg/m^2)	43.4 ± 6.6	42.9 ± 6.8
WHR	0.88 ± 0.07	0.89 ± 0.08
FM (%)	46.0 ± 6.6	45.0 ± 5.2
FFM (%)	53.9 ± 6.6	55.1 ± 5.9
REE (kcal/24 h)	1826.3 ± 362.0	1821.3 ± 324.6
REE/kgFFM (kcal/24 h)	31.0 ± 30.3	29.9 ± 29.5
Caloric intake (kcal/24 h)	2843.2 ± 1386	3148 ± 1551
TSH (μU/ml)	6.4 ± 2.7	2.1 ± 1.1*
FT_4 (pg/ml)	11.8 ± 2.4	12.3 ± 2.2
Leptin (ng/ml)	43.1 ± 18.0	42.9 ± 22.8
Total cholesterol (mg/dl)	216.9 ± 44.1	213.8 ± 40.9
HDL (mg/dl)	51.0 ± 13.6	48.9 ± 12.2
LDL (mg/dl)	133.1 ± 43.1	133.4 ± 35.2
Triglycerides (mg/dl)	155.9 ± 72.1	155.7 ± 72.3

* $p < 0.001$.

Methods

REE was assessed with a computerized, open-circuit, indirect calorimetry system that measured resting oxygen uptake and resting carbon dioxide production using a ventilated canopy (Sensormedics, Milano, Italy). REE was measured at 8:00 AM after an overnight fast in a comfortable and thermoregulated (22 °C to 24 °C) room with only the investigator and the patient present. After a 10-minute steady-state period, values were recorded each minute for 30 minutes; the mean value was expressed as kilocalories per 24 hours.

FM and FFM, expressed as percentage of total body mass (FM% and FFM%, respectively), were assessed by BIA (101/S; Akern, Firenze, Italy) the morning after overnight fasting and after voiding. The two vector components of impedance (i.e., resistance and reactance) were obtained by single measurements; before each testing session, the external calibration of the instrument was checked with a cali-

Table 2. Multiple regression model with REE/kgFFM as the dependent variable in obese patients with SH and in the control group with NTF

	SH		NTF	
Variables	**Standardized β coefficients**	***p***	**Standardized β coefficients**	***p***
FM (%)	0.718	0.000	0.420	0.000
BMI (kg/m^2)	−0.314	0.000	−0.129	0.286
WHR	0.317	0.000	0.128	0.272
Age (years)	−0.323	0.001	0.081	0.435
TSH (μU/ml)	−0.200	0.007	0.026	0.796
Leptin (ng/ml)	−0.100	0.265	0.311	0.017
FT_4 (pg/ml)	0.017	0.816	0.071	0.475
Caloric intake (kcal/24 h)	−0.103	0.193	0.026	0.810

bration circuit of known impedance value. The mean coefficient of variation was 1% for within-day and 3% for weekly intraindividual measurements in the steady-state condition in either site and 2% for interoperator variability. Total body water and FFM were derived from equations by Lukaski et al. (11,12).

Body fat distribution was estimated by WHR. The waist circumference was taken at the largest standing horizontal circumference between the ribs and the iliac crest; the hip circumference was taken at the largest standing horizontal circumference of the buttocks. Total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides were measured by an enzymatic method; TSH and FT_4 levels were determined by immunoenzymatic methods (DPC, Los Angeles, CA). Serum leptin levels were measured by radioimmunoassay using reagents supplied by Linco Research (St. Louis, MO). In this assay, the detection limit was 0.15 ng/ml; the intra-assay precisions (coefficient of variation) were 2.2% (6 ng/ml), 2.7% (25 ng/ml), and 5.9% (62.8 ng/ml), and the interassay precisions from 10 different runs of three patients' serum samples were 4.3%, 4%, and 6.9% at concentrations of 5.1, 21, and 56.2 ng/ml, respectively. In 32 lean subjects (BMI of 18 to 25 kg/m^2) the reference limits (2.5% to 97.5%) were 0.98 to 5.17 ng/ml in men and 2.6 to 17.4 ng/ml in women.

Statistical Analysis

Comparisons between means were analyzed by independent *t* test or Mann–Whitney test as appropriate to the distribution of the variables. A multiple regression model was used to assess the relationship between REE expressed for kilograms of FFM (REE/kgFFM) and TSH after controlling for variables known to influence REE. Potential confounding factors and collinearity between variables were also accounted for. Differences were accepted as significant at $p < 0.05$.

The release 9 of Statistical Package SPSS (SPSS Inc., Chicago, IL) was used for calculation.

Results

By selection, sex distribution and mean values for age and BMI did not differ significantly between SH patients and the control group; the TSH levels of the SH group were significantly higher ($p < 0.001$) than the levels of the control group, whereas FT_4 levels were not different (Table 1). The two groups did not differ significantly in caloric intake or for the values of FM and FFM, total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides. In addition, the values of REE were not significantly different between the SH and control groups even when expressed as REE/kgFFM (Table 1).

In a multiple regression model (Table 2) with REE/kgFFM as the dependent variable and FM%, BMI, WHR, age, TSH, leptin, free thyroxine, and caloric intake as independent variables, FM% significantly correlated with REE/kgFFM in both groups. In the group of SH patients only, BMI, WHR, age, and TSH levels were significantly related to the dependent variable. In this group of SH patients only, BMI, WHR, age, and TSH levels were significantly related to the dependent variable. Together, FM%, BMI, WHR, age, and TSH explained 69.5% of the variability of REE/kgFFM in SH patients.

In an attempt to gain insight into the level of impairment of thyroid function that would determine differences in the variables under study within the SH group, patients were assigned to subgroups according to the presence of TSH levels less than or greater than 5.7 μU/ml (68 and 40 patients, respectively), a value representing 3 SD greater than the mean of our normal values for euthyroid obese subjects.

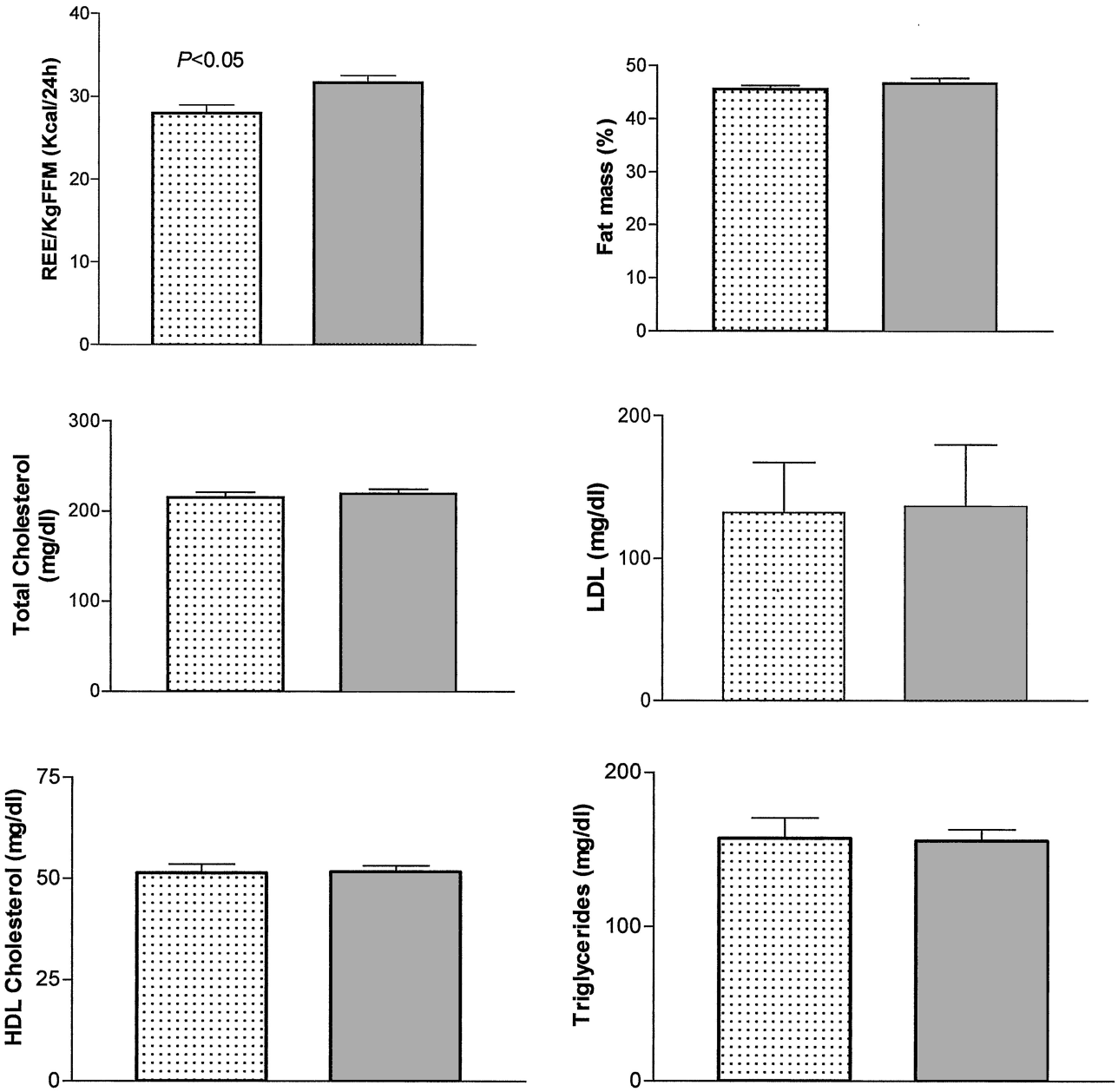

Figure 1. REE/kgFFM, FM, total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides (mean ± SE) in the group of obese patients with SH divided into two groups according to TSH level greater than (left bar) or less than (right bar) 5.7 μU/ml (i.e., 3 SD above the mean values of a reference population of obese subjects with NTF).

As shown in Figure 1, REE/kgFFM was significantly lower in the group with high TSH levels, whereas leptin levels, lipid values, and body composition were not different in the two groups.

Discussion

Our study shows that leptin levels, lipid profile, body composition, and REE/kgFFM do not differ between obese patients with euthyroidism and SH. TSH levels were an independent correlate of REE/kgFFM only in SH patients.

The problem of identifying peripheral indices of impaired activity of thyroid hormones seems of particular relevance in morbid obesity, a condition in which even a mild failure of thyroid function, as in SH, might aggravate some risk factors of cardiovascular disease and possibly contribute to maintenance of overweight. Our data indicate that direct assessment of REE is an early and sensitive parameter of thyroid hormone activity at the tissue level, as suggested by the observation that in the face of lower REE/kgFFM values, the lipid levels of patients with clearly elevated TSH

levels are still comparable with those of obese patients with NTF and with those of obese patients with a minor degree of SH.

A deficit of REE may be one of the factors leading to the development of obesity (13–15); thus, the evaluation of REE, which represents ~70% of the total energy expenditure, might prove useful in setting an appropriate level of caloric intake and physical activity in a weight-control program for obese patients. Our data show that obese patients with TSH levels clearly above the normal range (i.e., approximately ≥6 μU/ml) would require a direct evaluation of REE and probably should be started on L-thyroxine treatment. Although there are no data on the effect of the replacement therapy, it is reasonable to assume that L-thyroxine, by increasing REE (16), would improve the effectiveness of treatments aimed at reducing body weight.

The percentage of FM was not increased in the group of SH patients compared with controls and, within the group of obese SH patients, adiposity did not correlate with the degree of thyroid hypofunction. Because clinical studies indicate that hypothyroidism is associated with increased body fat (17,18), we conclude that thyroid function affects adiposity only when thyroxine concentrations fall below the normal range.

Our findings should also be considered in the context of the debate surrounding the problem of SH. The Clinical Association of American Endocrinologists states that "subclinical hypothyroidism may have important health consequences and treatment is advocated" (19); however, Arbelle and Porath (20) noted that there is no clear-cut strategy as to when replacement therapy should be started. There is some consensus that patients with TSH levels of ≥10 μU/ml with positive antibodies should be treated, but this is primarily intended to prevent overt hypothyroidism (21). SH seems to be an independent risk factor for atherosclerosis in elderly women (22); however, studies dealing with metabolic (23,24), cardiac (25), neurological (26), and psychological (27) parameters have demonstrated that SH is associated with abnormal findings only in a proportion of patients, and that the results of the treatment are often inconsistent especially in relation to lipid profile (23,28–32). Although our results were obtained in a particular population of patients with obesity, they confirm that SH is a heterogeneous condition in relation to the wide range of TSH values, despite normal levels of FT_4 (i.e., different degrees of a deficit of thyroid hormone effect at the tissue level) and to the variable sensitivity to thyroid hormones of the clinical and biochemical indices we have considered.

The inter-relationship between obesity and thyroid hormones in determining circulating levels of leptin is still a matter of discussion (33). Although the major determinants of leptin levels are gender and amount of fat, other factors are likely to be implicated in determining circulating leptin concentrations (34,35). Thyroid hormones exert a negative effect on leptin secretion in vitro (36,37); thus, leptin levels lower than normal in hyperthyroid patients and higher than normal in hypothyroid patients should be expected, but the data in the literature are largely contradictory (4,34,38,39).

In obese hypothyroid patients, serum leptin levels have been reported to be 30% higher than those of matched euthyroid obese patients, but normalization of thyroid function did not affect those levels (8). In this study, we did not find any difference in leptin levels between euthyroid and SH patients; thus, we believe that a mild deficit of thyroid function does not contribute to the variability of leptin levels in obesity.

The results of our study indicate that SH affects energy expenditure in obese patients only when TSH levels are clearly above the normal range; it does not modify body composition, lipid profile, and leptin levels. We suggest that, in these patients, evaluation of TSH levels may be useful to rule out a possible impairment of REE due to a reduced peripheral effect of thyroid hormones.

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