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Relationship of thyroid function with body mass index and insulin-resistance in euthyroid obese subjects

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ABSTRACT. ***Background and aims:*** **It is recognized that overt thyroid dysfunction is associated with weight changes, but the influence of a minor alteration of thyroid function remains unclear. This study aimed to further investigate the relationship between obesity and thyroid function and to examine the possible role of insulin resistance on the hypothalamic-pituitary-thyroid axis.** ***Methods and results:*** **Serum TSH and free T_4 (FT_4) levels, anthropometric and metabolic parameters were evaluated in 581 obese patients. In all patients TSH values progressively increased according to the severity of obesity and were positively correlated with body mass index (p=0.001, r=0.13) and waist circumference (p=0.02, r=0.11). Patients with insulin resistance showed higher TSH (1.8±1.0 *vs* 1.6±0.9 μUI/l; p=0.03) and lower FT_4 levels (13.8±2.3 vs 15.0±2.2 pmol/l; p<0.001), as compared with patients with normal insulin sensitivity. Moreover, TSH was positively correlated with fasting insulin (p<0.001, r=0.152) and homeostasis model assessment of insulin resistance (HOMA-IR; p<0.001, r=0.148), and negatively correlated with Quantitative Insulin Sensitivity Check Index (QUICKI; p<0.001, r=–0.148); FT_4 was negatively associated with fasting insulin (p<0.001, r=–0.287) and HOMA-IR (p<0.001, r=–0.295), and positively associated with QUICKI (p<0.001, r=0.295).** ***Conclusions:*** **A relationship between thyroid function and overweight/obesity condition seems to exist, mainly influenced by insulin resistance. Whether variations in TSH and/or thyroid hormones, within a normal range, can influence body weight or whether obesity *per se* can alter thyroid function cannot be stated so far. Further studies are needed to assess the link between thyroid function and body weight, by considering not only changes in thyroid hormones, but also body fat distribution, obesity duration and low-grade inflammation.**
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INTRODUCTION

It is well recognized that overt thyroid dysfunction is associated with significant weight changes, but the influence of minor alterations of thyroid function remains unclear. The majority of obese patients undergo assessment of their thyroid status, but only a minor percentage of them (10-19%) finally prove to have hypothyroidism (1, 2). Recent studies have focused on the possible relationship between slight abnormalities of thyroid function and changes in body weight, and particularly on the potential impact of differences in thyroid status in euthyroid subjects. The issue of an association between serum TSH or free thyroid hormones and body mass index (BMI) has been very recently addressed, but no definite conclusions have been provided (2-4). The influence of insulin resistance (IR), often present in obese patients, on the hypothalamic-pituitary-thyroid axis has also been taken into consideration, but conflicting results have been reported. A positive association between homeostasis model assessment (HOMA) and TSH has been reported (2, 5, 6), while a negative relationship between IR and free T_4 (FT_4) has been either found by some authors (5-7) or denied by others (2, 8). As the association between serum TSH and insulin levels or insulin sensitivity has been described in lean euthyroid subjects (9) and also in hyper- and hypothyroidism (10, 11), the influence of insulin on thyroid function still remains uncertain.

The present study aimed to further investigate the relationship between obesity and thyroid function and to examine the possible role of IR on the pituitary-thyroid axis in a large group of 581 obese subjects attending our Endocrinology and Diabetology Units.

MATERIALS AND METHODS

Subjects

The study group included 581 (436 females, 145 males) overweight and obese patients (BMI 37.0±6.5 kg/m^2, age 39.8±13.7 yr, mean±SD) consecutively referred to the Day Hospital of Endocrinology and Diabetology Units of the I.R.C.C.S. Policlinico San Donato, San Donato Milanese and of the Ospedale Maggiore, Policlinico I.R.C.C.S., Milan, Italy between 2004 and 2007. According to obesity BMI criteria recommended by the World Health organization (WHO) (12), our population was divided into four groups: 61 patients were overweight (BMI 28.7±1.0 kg/m^2), 201 had 1st degree obesity (BMI 32.6±1.4 kg/m^2), 151 had 2nd degree obesity (BMI 37.1±1.4 kg/m^2) and 168 had 3rd degree obesity (BMI 45.2±5.2 kg/m^2). The presence of metabolic syndrome was defined according to the National Colesterol Education Program – Adult Treatment Panel III (NCEP ATP III) (13).

Exclusion criteria included known or newly diagnosed thyroid disorders, other endocrine diseases, diabetes mellitus, neoplasms, acute or chronic inflammatory diseases. The WHO criteria were used to diagnose diabetes mellitus (14). An informed consent was obtained by all subjects and the study was approved by the institutional Ethics Committee.

Key-words: Obesity, TSH, thyroid hormones, insulin resistance, BMI, overweight.

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All patients were evaluated by medical history, physical examination and biochemical parameters. Anthropometric parameters were measured by standard procedures, including weight, height, waist and hip circumferences with calculation of BMI and waist/hip ratio (WHR). Waist circumference was taken at the level of umbilicus and hip circumference at trochanter level. Systolic and diastolic blood pressure were assessed according to the European Society of Hypertension and European Society of Cardiology Guidelines for the Management of Arterial Hypertension (15).
All subjects had fasting blood samples taken between 08.00 and 09.00 h to evaluate glucose, insulin, total cholesterol, HDL cholesterol, triglycerides, TSH (normal range: 0.26-5 μUI/l), FT_4 (normal range: 9-20 pmol/l).
Glucose levels were evaluated at baseline and at 120 min after 75 g oral glucose load (2 h-OGTT).

Assay

Serum TSH and FT_4 concentrations were measured using the AutoDELFIA technique (Perkin–Elmer-Life Sciences, Wallac Oy, Turku, Finland) and by Immulite 2000 (Siemens Medical Solutions Diagnostics, Los Angeles, CA, USA).
Insulin was measured by an immunoenzymatic one-step assay (Medgenics Diagnostics, Belgium) and glucose, total cholesterol, HDL cholesterol, triglycerides were measured by standard laboratory methods. IR was calculated by the homeostatic model assessment (HOMA-IR) and Quantitative Insulin Sensitivity Check Index (QUICKI).
HOMA-IR is a computer-solved model used to predict the degree of IR starting from fasting plasma insulin (FI) and glucose concentration (FG): IR=FI (μU/l) × FG (mg/dl)/405 (16). QUICKI was calculated as 1/[log FG (mg/dl)+log FI (μUI/ml)] (17). We defined insulin-resistant patients with HOMA-IR>2.5, and QUICKI<0.357.

Statistics

All results are expressed as mean±SD. Comparison of continuous variables among groups was done by using Student's t-test or one-way analysis of variance (ANOVA), with Bonferroni multiple comparison test whenever appropriate. Bivariate correlations between variables were tested by using Pearson correlation test. Multivariate linear regression analysis was performed with stepwise method, using $p<0.05$ as criteria to enter and $p>0.10$ as criteria to remove variables from the model. Values of $p<0.05$ were considered statistically significant.

Table 1 - *Main anthropometric, biochemical and hormonal parameters in 581 overweight and obese patients.*

	Mean±SD
Age (yr)	39.8±13.7
BMI (kg/m^2)	37.0±6.5
Waist circumference (cm)	107.4±14.7
Waist/hip ratio	0.8±0.1
Fasting plasma glucose (mg/dl)	91.0±11.3
2-h post load plasma glucose (mg/dl)	118.7±30.4
Fasting plasma insulin (mUI/l)	17.4±13.9
HOMA-IR	4.0±3.4
QUICKI	0.3±0.03
Total cholesterol (mg/dl)	206.1±94.9
Triglycerides (mg/dl)	132.6±82.3
HDL-cholesterol (mg/dl)	50.8±13.8
TSH (mUI/l)	1.8±1.0
FT_4 (pmol/l)	14.2±2.3

BMI: body mass index, HOMA-IR: homeostasis model assessment of insulin resistance; QUICKI: quantitative insulin-sensitivity check index; FT_4: free T_4.

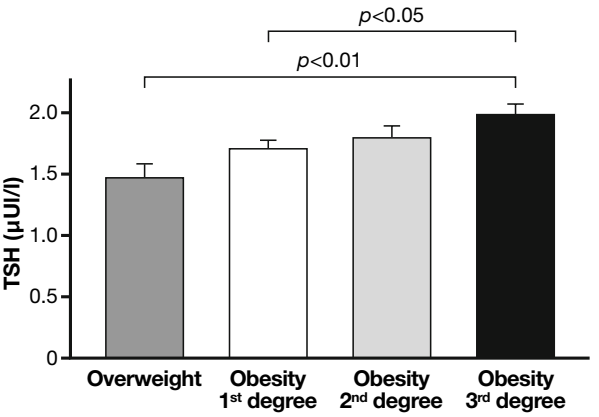

Fig. 1 - *Serum TSH levels in 581 patients affected with overweight and different degrees of obesity. TSH values significantly increased according to the severity of obesity (one-way analysis of variance p=0.003). Dunn's multiple comparison test: overweight vs 3rd degree of obesity p<0.01, 1st degree of obesity vs 3rd degree of obesity p<0.05. Overweight: BMI 25-29.9 kg/m^2; 1st degree of obesity: BMI 30-34.9 kg/m^2; 2nd degree of obesity BMI 35-39.9 kg/m^2; 3rd degree of obesity BMI≥40 kg/m^2.*

RESULTS

Table 1 shows the main anthropometric, biochemical and hormonal parameters found in the 581 overweight and obese patients.
Impaired fasting glucose (IFG) was found in 6.4% of our population and impaired glucose tolerance (IGT) in 21.6% of the 581 patients. Arterial hypertension was present in 51.2% of subjects and dyslipidemia in 50.2%. According to NCEP-ATP III criteria, 65% of patients were affected by metabolic syndrome.
In all patients serum TSH values progressively increased according to the severity of obesity (overweight: 1.5±0.8 μUI/l; 1st degree 1.7±1.0 μUI/l; 2nd degree 1.8±1.0 μUI/l and 3rd degree 2.0±1.0 μUI/l; $p=0.003$ by ANOVA) (Fig. 1). Conversely, no difference in FT_4 values among the four groups was found (overweight: 14.7±2.6 pmol/l; 1st degree 14.1±2.2 pmol/l; 2nd degree 13.9±2.4 pmol/l and 3rd degree 14.4±2.4 pmol/l; $p=0.2$).
Moreover, TSH levels were positively correlated with BMI ($p=0.001$, r=0.13) and waist circumference ($p=0.02$, r=0.11), while FT_4 levels were negatively correlated with WHR ($p=0.005$, r=–0.16).
No correlation was found between the values of TSH and age, and FT_4 levels and age.
It is to note that patients with insulin-resistance (61.1%) showed higher serum TSH (1.8±1.0 *vs* 1.6±0.9 μUI/l; $p=0.03$) and lower serum FT_4 levels (13.8±2.3 *vs* 15.0±2.2

pmol/l; $p<0.001$), as compared with patients with normal insulin sensitivity (Fig. 2).
In addition, TSH was positively correlated with fasting insulin ($p<0.001$, r=0.152) and HOMA-IR ($p<0.001$, r=0.148). Moreover performing bivariate analysis between TSH and HOMA-IR, a difference in r values between genders (males r=0.247, $p<0.05$; females r=0.137, $p<0.05$) was found. TSH values were negatively correlated with QUICKI ($p<0.001$, r=–0.148); FT_4 levels were negatively associated with fasting insulin ($p<0.001$, r=–0.287), HOMA-IR ($p<0.001$, r=–0.295) and positively associated with QUICKI ($p<0.001$, r=0.295).
Multiple linear regression analysis showed that HOMA-IR (B=0.041±0.012, $p=0.001$), BMI (B=0.014±0.007, $p=0.043$) and age (B=–0.009±0.003, $p=0.004$) are independent predictors of TSH values. Moreover HOMA-IR (B=–0.013±0.002, $p=0.0001$) and age (B=–0.001±0.001, $p=0.035$) are independent predictors of FT_4 levels.
The dyslipidemic patients (50.2% of cases) showed higher serum TSH levels (1.8±0.9 *vs* 1.6±0.9 µUI/l, $p=0.04$) and lower serum FT_4 levels (13.8±1.2 *vs* 14.5±1.2 pmol/l, $p=0.003$), than those without lipid alterations.
Regarding glucose homeostasis and blood pressure, no differences in serum TSH and FT_4 levels were found between patients with IFG and/or IGT and those with normal glucose metabolism, as well as in hypertensive patients as compared with normotensive (data not shown).
No correlation was found between the values of TSH and total cholesterol, tryglicerides, fasting glucose, 2 h-OGTT glucose, systolic and diastolic blood pressure.
In addition, no differences were found in serum TSH (1.9±0.1 *vs* 1.7±0.9 µUI/l) and FT_4 levels (13.6±1.2 *vs* 12.8±1.2 pmol/l) in patients with and without metabolic syndrome.

DISCUSSION

In the present study, performed on a wide population of 581 obese and overweight patients, an association between TSH values ad BMI was found. To our knowledge, this is the largest population recruited in an area of northern Italy, i.e. Milano and its surroundings, where the iodine uptake is normal. The site of recruitment may account for some differences with previous data obtained in southern Italy (7). In fact, at variance with De Pergola et al. (7) we observed a progressive increase in TSH values also when dividing our patients according to obesity degree. Particularly, patients with 3rd degree obesity showed significantly higher TSH values than those with a lower degree of obesity.
A clear association between TSH and BMI had been previously found both in a very wide general population study in Denmark (3) and in a small group of severly obese women (5). At variance, Michalaki et al. did not find any relationship between TSH and BMI in obese patients recruited in Greece, an iodine sufficient country (2). Thus, it is not yet clear whether obesity *per se* may influence thyroid function or whether small differences in thyroid function, even in a range of normality, might affect body weight.
A relevant finding in our study is concerned with the strong correlation between thyroid function and IR. In fact, the HOMA index was positively correlated with TSH and negatively with FT_4 levels, the reverse was found for QUICKI index, in agreement with previous data in obese women (2, 5) and also in a cohort of normal weight subjects (6). It is of interest that experimental studies showed that insulin induces the activity of thyroxine-5'-deiodinase, converting T_4 to T_3, in primary cultures of rat hepatocytes (18] and that brain insulin receptors may control body weight and homeostasis (19, 20). Nonetheless, a direct effect of insulin or IR on thyroid function in humans has not been demonstrated so far.
As far as FT_4 levels are concerned, the mildly lower levels in insulin-resistant patients are related to the finding of an increase in TSH values, as recently reported (5, 7). Also in the general population it has been demonstrated that subjects with HOMA in the highest tertile had lower FT_4 levels than those with HOMA in the lowest tertile and that TSH values were higher, though not significantly, in subjects with more elevated HOMA levels (6).
Nowadays, direct actions of insulin or IR on thyroid hormones synthesis and metabolism are not known. A possible interaction between thyroid function and environmental factors has been suggested in obese subjects. In fact, the exposition to organochlorine, compounds stored in the adipose tissue, could affect thyroid hormones synthesis in obesity. These compounds can accumulate into the food chain and are deposited in adipocytes (21); they may impair thyroid status by influencing T_3 and T_4 secretion. The observation that organochlorines cause le-

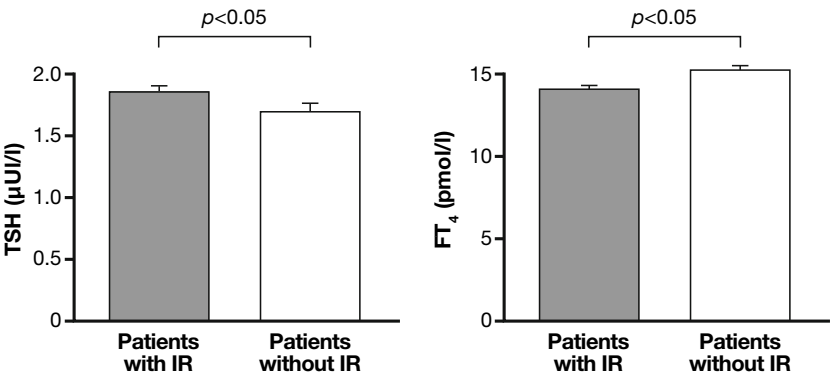

Fig. 2 - *Serum TSH and free T_4 (FT_4) levels in patients with and without insulin-resistance (IR). We defined insulin-resistant patients with homeostasis model assessment of insulin resistance (HOMA-IR) >2.5.*

sions in thyroid follicles by impairing the synthesis and secretion of T_4 (22-24) might explain the lowering of FT_4 levels with compensatory TSH increase in obese patients, mainly with IR and a greater amount of abdominal adipose tissue. It is of interest the recent observation by Alevizaki et al. that also subcutaneous fat accumulation is associated with higher TSH and lower FT_4 levels (25).

As far as the frequent alterations of lipidic profile in obese subjects are concerned, they are consistent with the presence of a metabolic syndrome. At variance with the population-based HUNT study (Nord-Trøndelag Health Study) performed on 30,656 normal and obese subjects (26), in the present series the mild variations of thyroid function did not seem to exert harmful effects on lipid profile and to be of clinical significance.

Although a positive association between serum TSH and blood pressure within the normal TSH range has been recently reported in normal and hypertensive subjects (27, 28), in our limited experience no influence of TSH and FT_4 levels on systolic and diastolic blood pressure was found and no relation of visceral obesity with hypertension, as recently reported (29), was observed.

In conclusion, our results confirm the existence of a relationship between thyroid function and overweight/obesity status, mainly influenced by IR, a factor that reflects both intra-abdominal fat deposition and obesity duration. Whether variations in TSH and/or thyroid hormones, within a normal range, can influence body weight or whether obesity *per se* can alter thyroid function cannot be stated so far. Further studies are needed to assess the link between thyroid function and body weight, by considering not only changes in thyroid hormones, but also body fat distribution, obesity duration and low-grade inflammation.

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