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Short report

Increased TSH in obesity: Evidence for a BMI-independent association with leptin

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Abstract

Aim. – This study aimed to determine whether the association between thyroid-stimulating hormone (TSH) and body mass index (BMI) is related to leptin concentration in obese individuals.

Methods. – Plasma TSH and leptin assays were performed in 800 consecutive patients, hospitalized for a nutritional checkup, with a BMI ≥ 30 kg/m². Various anthropometric, hormonal and metabolic parameters, including age, weight, BMI, insulin, leptin and TSH, were measured or calculated. Univariate and multivariate regression analyses were performed to identify any significant relationships between these parameters. Also, characteristics of the patients in the lowest and highest quartiles of TSH distribution were compared.

Results. – TSH was positively correlated with both BMI and leptin. When multiple regression analysis was performed, TSH and leptin maintained a significant association independent of BMI. Patients in the fourth quartile of TSH distribution displayed higher BMI and higher leptin levels in comparison to the first quartile.

Conclusion. – Our study has confirmed an increase in TSH in conjunction with BMI in obese subjects. This increase was correlated with leptin independently of BMI. It is hypothesized that the increase in TSH observed in obese subjects was the consequence of both fat mass accumulation and a positive energy-balance.

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Keywords: Leptin; TSH; Obesity; Energy-balance

1. Introduction

Obesity is a major worldwide health problem with an increasing prevalence. In 2013, more than a third of the world's population was either overweight or obesity [1]. Yet, the pathophysiology of the condition remains unclear. Identifying hormonal targets involved in the condition may help in the management of obese patients.

As thyroid hormones are involved in the regulation of energy-balance, evaluation of thyroid function in obese subjects has been widely investigated [2]. It has been previously described that thyroid-stimulating hormone (TSH) was slightly increased in obese populations [3]. However, the exact mechanisms involved in such increased TSH levels, as well as its physiological relevance, are as yet undetermined.

Several authors have suggested that leptin actions could underlie the association between obesity and increased TSH levels [4]. However, to our knowledge, such an association has not been previously reported in an obese population. Thus, the aim of the present study was to determine the associations between body mass index (BMI), TSH and leptin plasma levels in a large

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cohort of obese subjects, and to evaluate their physiological relevance.

2. Methods

2.1. Study population

This was a single-centre, retrospective observational study using prospective recruitment. Consecutive adult subjects hospitalized in the Department of Endocrinology (Diabetes and Nutrition) at Lyon South Hospital in Pierre-Bénite, France, for nutritional evaluation of obesity (BMI > 30 kg/m²) were screened between 2009 and 2011. Plasma leptin and TSH levels were consistently determined during these nutritional checkups. Patients with a previous history of thyroid diseases or bariatric surgery were excluded. Ultimately, 800 obese patients were included in our study. Their initial data were collected retrospectively using a specifically dedicated computerized database.

2.2. Measurements

For each included subject, age, gender, body weight, height, BMI, TSH, leptin, triacylglycerols, total cholesterol, fasting plasma glucose, HbA_{1c}, fasting plasma insulin, homoeostasis model assessment of insulin resistance (HOMA-IR) and C-reactive protein (CRP) were measured, calculated or assessed. Blood samples were drawn in the morning after an overnight fast. TSH concentration was measured by immunoradiometric assay (IRMA; Beckman-Coulter, Villepinte, France), using a proposed range of normal values from 0.29 to 3.80 mIU/L. Leptin was measured by enzyme-linked immunosorbent assay (ELISA; BioVendor, Brno, Czech Republic).

2.3. Statistical analysis

Results are presented as means ± SEM for all parameters, and $P < 0.05$ was considered statistically significant. Normality of parameter distribution was checked by Shapiro–Wilk test, and Student's *t*-test was used to compare variables of the first and fourth quartiles of the study population according to TSH distribution. Categorical differences were tested with the Chi² test. Significant relationships between study parameters were evaluated by Spearman's non-parametric correlation coefficient. Multiple regression analysis was performed to test the combined effects of different variables, including gender and age, on TSH level. All statistical analyses were performed using XLSTAT-Pro 2013 (Addinsoft, Paris, France) and MedCalc 9.2 (Ostend, Belgium) statistical software.

3. Results

Characteristics of the study population are presented in Table 1. A total of 160 obese subjects, representing 20% of the study population, exhibited plasma TSH values > 3.80 mIU/L, the upper limit of the normal range, with a mean TSH value of 5.3 ± 0.1 mIU/L for that quintile. To determine the characteristics of this obese population with slightly increased TSH

Table 1
Characteristics of the study population.

	Mean ± SEM	95% CI
Female gender [n (%)]	554 (69)	–
Age (years)	44.1 ± 0.5	43.1–45.0
Weight (kg)	112.6 ± 0.9	111.1–114.5
Height (cm)	165.1 ± 0.3	164.4–165.7
Body mass index (kg/m ²)	41.3 ± 0.3	40.8–41.8
TSH (mIU/L)	2.8 ± 0.1	2.7–2.9
Leptin (ng/mL)	56.0 ± 1.3	52.9–58.1
Triacylglycerols (mmol/L)	1.90 ± 0.05	1.80–2.01
Total cholesterol (mmol/L)	5.33 ± 0.04	5.25–5.42
Fasting plasma glucose (mmol/L)	5.70 ± 0.06	5.58–5.82
HbA _{1c} (%)	6.09 ± 0.04	6.01–6.17
Fasting plasma insulin (mU/L)	12.3 ± 0.6	11.00–13.63
HOMA-IR	3.4 ± 0.2	2.89–3.88
CRP (mg/L)	8.7 ± 0.4	7.97–9.41

TSH: thyroid-stimulating hormone; HOMA-IR: homoeostasis model assessment for insulin resistance; CRP: C-reactive protein.

Table 2
Body mass index (BMI) and leptin levels by quartile of thyroid-stimulating hormone (TSH).

Quartile	TSH (mIU/L)	Leptin (ng/mL)	BMI (kg/m ²)
1	1.19 ± 0.02	47.7 ± 2.0	40.4 ± 0.5
2	2.05 ± 0.02	54.1 ± 2.9	40.5 ± 0.5
3	2.92 ± 0.02	56.3 ± 2.2	42.0 ± 0.6
4	4.97 ± 0.10	64.0 ± 3.1	42.3 ± 0.6

Data are presented as means ± SEM.

levels, the whole study population was divided into quartiles according to TSH levels (Table 2). Significant differences were observed for weight and BMI, which were both significantly higher in those in the fourth vs. the first quartile of TSH (weight: 116.2 ± 1.9 kg vs. 110.1 ± 1.5 kg, $P = 0.013$; and BMI: 42.3 ± 0.6 kg/m² vs. 40.4 ± 0.5 kg/m², $P = 0.007$, respectively). The most striking difference was seen in the mean value of plasma leptin, which showed a +34.5% difference between the first (47.7 ± 2.0 ng/mL) and fourth (64.0 ± 3.1 ng/mL) quartiles. It is noteworthy that this difference was not due to gender distribution in the first vs. fourth quartiles (females: 66% vs. 73%, respectively; $P > 0.05$). Metabolic and inflammatory features, including fasting glucose, insulin, HOMA-IR, triacylglycerols and CRP, displayed no significant differences between quartiles of TSH.

Crude coefficients of correlation between TSH levels and anthropometric or metabolic characteristics of the whole study population were first assessed in simple linear regressions, then in multiple linear regressions. Few parameters were significantly associated with TSH levels: TSH was positively correlated with weight ($P < 0.05$), BMI ($P < 0.05$) and leptin

($P < 0.001$), and negatively correlated with age ($P < 0.05$). It is worth noting that the strongest crude linear correlation was between TSH and leptin ($\rho = 0.146$). Also, as expected, leptin was positively and linearly correlated with BMI ($\rho = 0.47$, $P < 0.0001$). After stratification analyses according to gender, TSH remained positively correlated with leptin in both men and women ($\rho = 0.199$, $P < 0.01$, and $\rho = 0.092$, $P < 0.05$, respectively). All parameters significantly associated with TSH in the univariate analysis were also analyzed in a multiple regression model. Using multiple linear regression analysis with TSH as the dependent variable, and age, gender, BMI and leptin as independent variables, it was observed that TSH maintained a positive linear correlation with leptin ($P = 0.0019$) independent of all other parameters. The other analyzed parameters, such as gender, triacylglycerols, total cholesterol, fasting plasma glucose, HbA_{1c}, fasting plasma insulin, HOMA-IR and CRP, displayed no significant association with TSH levels even after multivariate analysis.

4. Discussion

The present study provides evidence that TSH levels are significantly, positively and linearly associated with BMI and leptin in a randomly selected obese population. Moreover, TSH variability was mainly explained by leptin independently of BMI, thereby suggesting a link between the hypothalamus–pituitary–thyroid (HPT) axis and adiposity.

Also observed in our study was a weak, but significant, positive correlation between serum TSH levels, on the one hand, and both weight and BMI, on the other. It had previously been reported that TSH tends to increase with body-fat accumulation in the general population. In a recent meta-analysis, de Moura Souza and Sichiari [5] reported a positive relationship between TSH and measures of adiposity in 18 out of 29 reviewed studies. Our present study also found a significant correlation between TSH and leptin levels ($\rho = 0.146$, $P < 0.0001$), which remained significant after adjusting for BMI. Currently, there is evidence that the HPT axis is regulated, at least in part, by leptin. However, while such a correlation between leptin and TSH has been previously reported, it has never to our knowledge been ascertained in such a large cohort of obese subjects [6]. Leptin, the plasma levels of which correlate with the percentage of body-fat mass, is a hormone secreted by adipocytes to inform the hypothalamus of energy reserves. The strength of the linear association between leptin and BMI in our large cohort of obese subjects was surprisingly not particularly high ($\rho = 0.47$, $P < 0.0001$). While the fat mass stored in adipocytes is one of the main determinants of leptin levels, it should also be noted that leptin secretion rapidly declines with food restriction or weight loss in both clinical and preclinical studies [7]. Thus, leptin levels depend on the body-fat mass, but also on energy-balance status. In our study, TSH correlated with leptin independently of BMI, suggesting that TSH might be associated with energy-balance status rather than adiposity.

Experimentally, leptin stimulates pituitary TSH secretion [8]. Indeed, it has been shown that leptin can regulate thyrotropin-releasing hormone (TRH) expression and secretion [9] through

mediation of input from the arcuate nucleus to TRH neurons in the paraventricular nucleus (PVN) [10]. In addition, the HPT axis is also indirectly regulated by leptin actions in the melanocortin pathway, as alpha-melanocyte-stimulating hormone (α -MSH) stimulates, while agouti-related protein (AgRP) blocks, TRH release [11]. Furthermore, leptin has direct effects on TRH neurons, regulating its synthesis not only by upregulating the expression of pro-TRH genes in the PVN [12] and influencing the feedback regulation of TRH-secreting neurons by thyroid hormones, but also by increasing promoter activities of prohormone convertase (PC) 1/3 and PC2, which are essential for activation of TRH from pro-TRH [13]. Thus, an increase in leptin induced by a positive energy-balance in obesity could stimulate TSH secretion which, in turn, could increase free thyroid hormones, thermogenesis and, finally, energy expenditure, thereby limiting further body weight gain. This hypothetical regulation loop may constitute a new insight into the cross talk between fat mass and the pituitary and thyroid glands in the maintenance of energy homeostasis. Thus, our present data are in line with the previous hypothesis of a hypothalamus–pituitary–adipose axis [14].

The main strength of the present study, which demonstrates a weight-independent association between TSH and leptin in obesity, is the size and diversity of the study population, which included all consecutive obese subjects assessed over 2 years, with the exception of those with a medical history which might affect TSH or leptin levels. In particular, patients who had undergone bariatric surgery were excluded, as this treatment induces notable leptin decreases related to weight loss and food restriction [15]. However, data on energy status (weight gain or loss) as well as data on free thyroid hormones are lacking in our study, and need to be addressed in future research to reinforce our conclusions. Moreover, smoking can slightly reduce both TSH [16] and leptin [17] levels, whereas smoking status was not assessed in our present cohort.

Nevertheless, our study has confirmed the positive relationship between TSH and BMI in obesity, and our findings have moved the research forward by demonstrating a positive relationship between leptin and TSH that was independent of BMI in a large cohort of obese subjects.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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