Obesity is associated with increased serum TSH level, independent of thyroid function

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Summary

Objective: To reinvestigate the relationship between circulating TSH levels and adiposity in a cohort of obese people, who have normal thyroid function.

Methods: Retrospective cross-sectional analysis was carried out on 226 euthyroid obese or overweight female patients. Thirty-nine female lean and euthyroid subjects (BMI <25 kg/m^2) were included in the study group. TSH, free thyroxine (FT4), free triiodothyronine (FT3), fasting plasma levels of insulin and glucose, homeostasis model assessment (HOMA) for insulin resistance (HOMA-IR) and insulin secretion (HOMA-β cell), body weight, height, body mass index (BMI) and waist circumference were assessed.

Results: Serum TSH levels were higher in the obese than in the lean subjects. In the study group (lean and obese subjects), there was a significant positive correlation between serum TSH and body weight (r = 0.231, p <0.001), BMI (r = 0.270, p <0.001), waist circumference (r = 0.219, p = 0.001), fasting insulin (r = 0.201, p = 0.002) and HOMA-IR (r = 0.201, p = 0.002); there was no correlation between serum FT4 and any of the parameters. A multivariate linear regression analysis revealed that only BMI (p = 0.012, 95% CI = 0.01–0.08) contributed significantly to the variance of TSH.

Conclusions: This study strongly supports existing, but contradictory evidence that serum TSH levels are positively correlated with the degree of obesity and some of its metabolic consequences in overweight people with normal thyroid function.

Key words: adiposity; TSH; thyroid function; obesity

Introduction

The eminent endocrine role of the pituitary hormone thyrotropin is to regulate the function of the thyroid gland. The serum level of thyrotropin (TSH) is a reliable index of the biological activity of thyroid hormones. In turn, as prime regulators of energy balance, the contribution of thyroid hormones to the maintenance of body weight has been the subject of numerous clinical studies. Measurement of serum levels of TSH has been a consistent component of the clinical studies on the relationship between thyroid function and adiposity. The conclusion from some of these studies has been that weight gain increases serum levels of TSH; yet, others showed no relationship between TSH and body weight [1–6].

Evidence emerging that thyrotropin induces adipogenesis and adipokine production directly, independent of the mediating influence of thyroid hormones on energy balance, prompted us to reinvestigate the relationship between circulating TSH levels, body weight and the metabolic consequences of adiposity in a cohort of obese people, with normal thyroid function. Our results provide circumstantial evidence that the pituitary gland, via thyrotropin may indeed contribute to the evolution of obesity, independent of any involvement of the thyroid gland.

Materials and methods

Subjects

Retrospective cross-sectional analysis was carried out on 350 obese or overweight patients referred to the Obesity Outpatient Clinic of the Department of Endocrinology and Metabolic Diseases at Pamukkale University Hospital in Denizli, Turkey between 2002 and 2003. Of these, 124 patients were excluded for any of the following reasons: male gender, history of thyroid disease, thyroid autoantibody positivity, abnormal thyroid hormone levels, history of radioiodine treatment, being on treatment with thyroid hormone, antithyroid drugs or any drug that might affect evaluation of thyroid status. Together, 226 female patients were consid-

ered eligible for this study. The mean age was 43 [12] years, the mean BMI 36 [6] kg/m², and the duration of obesity 17±3 years. Twenty-nine carried the diagnosis of type 2 diabetes mellitus, and of these, 23 patients were on treatment with acarbose, metformine and/or sulphonylureas. Six of the diabetic patients were newly diagnosed.

Patients were also assigned into 4 groups according to classification of obesity: preobese (n = 28, BMI 25–29.9 kg/m²), class I obesity (n = 93, BMI 30–34.9 kg/m²), class II obesity (n = 58, BMI 35–39.9 kg/m²) and class III obesity (n = 47, BMI <40 kg/m²).

We needed also subjects who had BMI <25 kg/m² to evaluate the effect of BMI on TSH level. We examined 100 volunteers of which 61 subjects were excluded for any of the following reasons: BMI ≥25 kg/m², history of thyroid disease, thyroid autoantibody positivity, abnormal thyroid hormone levels, being on treatment with thyroid hormone, antithyroid drugs or any drug that might affect evaluation of thyroid status and 8 subjects desisted from giving blood for blood testing. Thirty-nine female subjects were considered eligible for this study. The mean age was 40 [9] years, the mean BMI 22 [2] kg/m².

The subjects in the lean group gave written voluntary consent to participate in the study.

The study was reviewed and approved by the Human Subject Research Ethics Committee of the Pamukkale University Medical School. Informed consent was not required for retrospective analysis of records; the research database was not linkable to the subjects.

Study design

Serum levels of TSH, free thyroxine (FT4) and free triiodothyronine (FT3) were measured as indicators of thyroid function. As indicators of insulin action, fasting plasma levels of insulin and glucose were measured and submitted to homeostasis model assessment (HOMA) for insulin resistance (HOMA-IR) and insulin secretion (HOMA-β cell).

The formula used for calculating HOMA-IR was fasting plasma insulin (mU/l) × fasting plasma glucose (mmol/l)) / 22.5, and HOMA-β cell fasting plasma insulin (mU/l) × 20 / fasting plasma glucose (mmol/l) – 3.5 [7].

Anthropometrical measurements

Body weight (kg) and height (m) were measured while subjects wore light clothing and no shoes. BMI was calculated as weight divided by squared height (kg/m²). Waist circumference was measured at the level of the umbilicus.

Laboratory methods

Plasma glucose levels (mmol/l, fasting reference range 3.05–6.38) were measured by an autoanalyser (Beckman Coulter Lx-20, USA), using commercial kits (Beckman-Coulter, USA). Plasma levels of insulin (μIU/ml, fasting reference range 0.1–17), TSH (μIU/ml, reference range 0.27–4.2), FT4 (ng/dl, reference range 0.8–1.9), and FT3 (pg/ml, reference range 1.57–4.71), were determined by an immune analyser (Immulite 2000, USA). HOMA-IR cut-off value was 2.7 (>2.7 resistant, <2.7 sensitive). HOMA-β cell cut-off value was % 100.

Statistical analyses

All statistical analyses were performed using SPSS 9.0 software (SPSS Inc). Data are presented as means±SD. Correlation between measured parameters was assessed using the analytical method of partial correlation, and was adjusted for age by linear regression analysis. Comparison of TSH levels between groups of lean, preobese, class I, class II and class III obese subjects were performed with one-way ANOVA test. Multivariate linear regression with TSH as the outcome was used to show that BMI was correlated with TSH having adjusted for covariates including age, waist circumference, fasting glucose, fasting insulin, HOMA-IR and HOMA-β cell.

Results

Anthropometric and clinical characteristics of the subjects are shown in table 1. Serum TSH levels were higher in the obese than in the lean subjects; no significant difference was found in serum FT4 levels between the two groups. Fasting plasma insulin levels and HOMA-IR were higher in the obese subjects. HOMA-β cell was similar in the lean and obese subject groups.

When the study group was stratified according to the degree of adiposity (lean with BMI <25, preobese with BMI ≥25–<30, class 1 obesity with BMI 30–<35, class 2 obesity with BMI 35–<40, and class 3 morbid obesity with BMI ≥40), a gradation in serum TSH levels became evident, with corresponding degrees of significance when compared to the lean group: 1.37±0.63 μIU/ml (NS), 1.65±0.80 μIU/ml (NS), 1.70±0.94 (NS), and 1.99±0.95 μIU/ml (p = 0.019, %95 CI = (–1.18)–(–0.07)), re-

spectively. TSH levels increased with increasing degree of BMI.

In the study group, serum TSH was positively and significantly correlated with body weight (r = 0.231, p <0.001), BMI (r = 0.270, p <0.001), waist circumference (r = 0,219, p = 0.001), fasting insulin (r = 0.201, p = 0.002) and HOMA-IR (r = 0.201, p = 0.002); there was no significant correlation between serum FT4 and any of the parameters.

A multivariate linear regression analysis for the association between TSH and variables are shown in table 2. This analysis revealed that only BMI contributed significantly to the variance of TSH. This association was only slightly attenuated after additional adjustment for metabolic factors, including HOMA-IR, HOMA-β cell, fasting insulin and fasting glucose.

Discussion

Our study in a cohort of overweight people with normal thyroid function strongly supports the previously reported, but still contested positive correlation between serum TSH levels and the degree of

obesity. The significant correlation is corroborated by the inclusion of non-obese healthy people. Since all TSH values in all patients were – by definition – within normal range, a study of this type can only be

Table 1

Anthropometric and clinical characteristics of lean and obese subjects.

	Lean subjects	Obese subjects
N	39	226
Age (years)	40 (9)	43 (12)
Height (cm)	157 (6)	157 (6)
Weight (kg)	55 (6)	90 (16)
BMI (kg/m^2)	22 (2)	36 (6)
Waist circumference (cm)	72 (5)	96 (11)
Systolic blood pressure (mm/Hg)	106 (12)	125 (19)
Diastolic blood pressure (mm/Hg)	71 (9)	82 (11)
TSH (µIU/mL)	1.4 (0.6)	1.7 (0.9)
FT4 (ng/dL)	1.2 (0.2)	1.2 (0.4)
FT3 (pg/mL)	–	2.8 (0.7)
Fasting glucose (mmol/L)	4.9 (0.4)	5.9 (1.5)
Postprandial glucose (mmol/L)	–	6.57 (2.5)
Fasting insulin (µIU/mL)	7.8 (2.7)	12.4 (6.4)
HOMA-IR	1.7 (0.6)	3.2 (1.8)
HOMA-β cell	130 (79)	124 (128)

Data were given as mean (standart deviation)

Table 2

Multivariate linear regression analysis with TSH as dependent variable.

	Independent variable	Beta	t	P-value	95% Confidence interval
Model 1	Age	–0,108	–1,606	0,110	–0,018–0,002
	BMI	0,445	2,712	0,007	0,014–0,089
	Waist circumference	–0,183	–1,108	0,269	–0,032–0,009
Model 2	Age	–0,099	–1,419	0,157	–0,018–0,003
	BMI	0,426	2,580	0,011	0,012–0,087
	Waist circumference	–0,221	–1,322	0,188	–0,034–0,007
	HOMA-IR	0,112	1,505	0,134	–0,017–0,126
	HOMA-β	–0,025	–0,361	0,718	–0,001–0,001
Model 3	Age	–0,079	–1,087	0,278	–0,017–0,005
	BMI	0,417	2,519	0,012	0,011–0,086
	Waist circumference	–0,210	–1,244	0,215	–0,034–0,008
	HOMA-IR	–0,009	–0,024	0,981	–0,371–0,362
	HOMA-β	–0,075	–0,890	0,374	–0,002–0,001
	Fasting glucose	–0,023	–0,129	0,897	–0,012–0,011
	Insulin	0,158	0,462	0,645	–0,080–0,129

done with sufficient precision by using a highly sensitive third generation assay. The "normal range" of serum TSH is derived exclusively from its relationship with thyroid hormones in strictly euthyroid persons. One might assume that the interaction between TSH and adipose tissue occurs on a scale different from that involved in thyroid regulation.

Recent studies in man and other mammalian species have yielded convincing evidence that adipocytes and preadipocytes possess thyrotropin receptors [8–10]. The signal generated by thyrotropin in adipocytes is mediated by the activation of cAMP-dependent protein kinase [4]. Studies *in vitro* and *in vivo* demonstrate that the action of thyrotropin via its receptors in fat tissue induces differentiation of preadipocytes into adipocytes, and expansion of adipose tissue (adipogenesis) [8, 12]. Adipose tissue is a major endocrine gland, producing and releasing numerous adipokines, which have metabolic or inflammatory effects in other tissues, including the liver, muscle, pancreatic islet β-cells and the brain [13, 14]. Thyrotropin directly induces the synthesis and release of adipokines [15, 16], some of which control appetite (eg leptin) by acting on the brain.

The well-documented expression of thyrotropin receptors and transduction of the thyrotropin signal in adipocytes warrant the consideration that the positive relationship we observed in our study between serum TSH and adiposity has biological significance.

Based on their observation that receptors for many of the pituitary hormones are expressed in adipose tissue [10] proposed that a "hypothalamic-pituitary-adipose axis" exists. The positive relationship between serum TSH and adiposity would be consistent with this concept in a "downstream" sense. Yet, such an axis would require a feedback system, and hence the positive relationship between serum TSH and adiposity could also be interpreted in the reverse.

The increase in fat mass, in particular the visceral fat, leads to increased production and release of many of the adipokines [7]. Among the adipokines, extensive information is available on the inhibition of appetite by leptin, dominantly by acting on the hypothalamus. A positive correlation has been reported between serum levels of leptin and TSH [16, 18, 19].

Obesity, particularly visceral obesity, is associated with insulin resistance [20]. Thus, almost twofold increase in HOMA-IR in the obese group was expected. The fact that in our study HOMA-IR was positively correlated with serum TSH in the study group (lean and obese subjects in combination) suggests that the role played by thyrotropin in adipogenesis has a metabolic consequence. The positive correlation between serum TSH and fasting plasma insulin and lack of correlation with HOMA-β cell could be interpreted as lack of an influence of thyrotropin signal upon pancreatic islets and thus upon the increases in insulin release to compensate for insulin resistance.

As expected, in a cohort selected for euthyroid state, mean serum T4 levels were well within the normal range and very similar among lean and obese subjects. Serum T3 levels, available only of the obese subjects, were also well within the normal range. No statistical relationship existed between serum T4 and any of the parameters of adiposity. This lack of a correlation coincident with a positive correlation between serum TSH and adiposity would be consistent with a direct interaction of thyrotropin and adipose tissue in the regulation of body weight.

Our study was not designed to prove or disprove a direct role of thyrotropin in adiposity. It was at best an observational study, taking advantage of the availability of structured clinical information on a reasonably large cohort of people in a wide spectrum of adiposity. It is not known at the present time whether increased TSH levels favour the deposition of fat or, on the contrary, whether excessive accumulation fatty tissue increases TSH secretion. Among the important statements is, eg the presence of TSH receptors in adipose tissue. On the other hand, since TSH is correlated with obesity and obesity leads by itself to insulin resistance, it is obvious that TSH must necessarily be correlated with insulin resistance. Therefore, no cause- effect relationship can be constructed. Moreover, one needs to be careful not to overinterpret the role of the minimally increased TSH itself on metabolic events.

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