Circulating leptin levels are not influenced by thyroid status in hypothyroid and euthyroid women

Maciej Owecki [1], Ziad El Ali [1], Ryszard Waśko [1], Elżbieta Nikisch [2], Aleksandra Dziubandowska [1], Anna Sulikowska [1] & Jerzy Sowiński [1]

1. Department of Endocrinology, Metabolism and Internal Medicine, University of Medical Sciences in Poznań, Poland
2. Department of Informatics and Statistics, University of Medical Sciences in Poznań, Poland

Correspondence to: Maciej Owecki, MD., PhD.
Department of Endocrinology, Metabolism and Internal Medicine
ul. Przybyszewskiego 49, 60-355 Poznań, Poland
PHONE: +48 61 8691330
FAX: +48 61 8691682
EMAIL: mowecki@ump.edu.pl

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Abstract

OBJECTIVES: Leptin regulates body weight by suppressing food intake and increasing energy expenditure. Alterations in thyroid hormone levels are also associated with changes in body weight but the effect of thyroid hormone deficiency on serum leptin in humans is unclear.

DESIGN AND METHODS: The aim of this study was to measure leptin levels and to investigate their associations with thyroid hormones in 22 women with severe hypothyroidism after total thyroidectomy, and in a group of 22 healthy euthyroid control female subjects matched for age and body mass index (BMI). Their plasma leptin, free thyroxine, triiodothyronine and TSH were measured.

RESULTS: Leptin levels in subjects and controls were (pg/mL) 18761.64±16973.96 and 18729.19±18014.05, respectively, p=0.9; leptin did not correlate with free thyroxine, triiodothyroinine and TSH: r=0.1039 and p=0.6453, r=0.0113 and p=0.9602, and r=–0.0525 and p=0.8165 for leptin and FT4, leptin and FT3, and leptin and TSH, respectively in subjects; r=–0.00056 and p=0.9980, r=0.248727 and p=0.2643, and r=–0.046919 and p=0.8357 for leptin and FT4, leptin and FT3, and leptin and TSH, respectively in controls. Leptin levels did not differ between subjects and controls and they did not correlate with thyroid hormones.

CONCLUSIONS: Leptin levels are not influenced by hypothyroidism and do not correlate with thyroid hormones in euthyroid and hypothyroid women.

ORIGINAL ARTICLE

INTRODUCTION

Leptin, encoded by the *ob* gene, is a protein that regulates body weight by suppressing food intake and increasing energy expenditure (Campfield *et al*. 1995; Considine *et al*. 1995; Halaas *et al*. 1995; Sinha *et al*. 1996; Zhang *et al*. 1994). Serum leptin levels show a positive correlation with body fat, being increased in obesity (Considine *et al*. 1996; Hamilton *et al*. 1995; Lonnqvist *et al*. 1995) and decreased in states of severe malnutrition such as anorexia nervosa (Ferron *et al*. 1997). Therefore, leptin is an adipocyte-synthesized hormone, the role of which is to inform the brain of the amount of the adipose tissue present in the body (Jeanrenaud FR & Jeanrenaud B, 1996; Meier CA, 1996).

On the other hand, alterations in thyroid hormone levels are frequently associated with changes in body weight. Thus, patients with hypothyroidism usually show an increase in body weight, whereas, on the contrary, hyperthyroid patients usually lose weight (Ingbar, 1985). Consequently, weight gain in hypothyroidism might result in an increase of leptin concentration, whereas a decrease might occur in hyperthyroidism. Only few studies have thoroughly evaluated the associations between leptin and thyroid status. Leptin levels have been reported to be decreased in hypothyroid patients and unchanged in hyperthyroidism. (Valcavi *et al*. 1997) Moreover, some studies have shown that leptin may regulate TSH pulsatility and circadian rhythmicity in men (Mantzoros *et al*. 2001) and that leptin administration can blunt the food deprivation induced increase of cortisol and decrease in thyroid and gonadal hormone levels in mice. (Ahima *et al*. 1996). Furthermore, administration of leptin reversed the decrease of circulating T3 and T4 levels in humans during a period of reduced body weight.

In spite of all the data mentioned above, however, the effect of thyroid hormone deficiency on serum leptin levels in humans is unclear. Most studies have been performed in small groups of healthy men, or in animals. Therefore, the aim of this study was to measure leptin levels and to evaluate their associations with thyroid hormones in women with severe hypothyroidism after total thyroidectomy, and in a group of healthy euthyroid control female subjects matched for age and body mass index (BMI).

MATERIALS AND METHODS

The study group consisted of 22 consecutive female hypothyroid patients and 22 age- and BMI-matched healthy euthyroid women as controls (mean age 49.9±15.0 and 43.7±10.1 yrs, respectively, p=0.07). Prior to this study, all hypothyroid subjects had undergone total thyroidectomy and radioiodine ablation for differentiated thyroid cancer. Then, they were admitted to the Department of Endocrinology for control search for tumor rests and this study was performed under these circumstances. In none of the subjects recurrence was demonstrated. Each subject ceased levothyroxine treatment six weeks prior to admission to enable radioiodine tests. None of the subjects or controls showed the features of the metabolic syndrome according to IDF criteria, or presented with diabetes mellitus. None had a history of alcohol overconsumption. None of the subjects was completely sedentary, or involved in athletics. All subjects were examined in the morning (at 08:00 a.m.) after an overnight fast.

All subjects were examined physically, and their body mass index (BMI) was measured with the formulation: body mass (kg) divided per square height (m). Physical signs confirming thyroid hypofunction included facial appearance, heart rate and rhythm, skin temperature and texture of skin and hair, as well as a scar on the neck related to previous thyroidectomy, and lack of the thyroid gland in ultrasound examination. Hypothyroidism was diagnosed on the basis of history of thyroid ablation, clinical symptoms and laboratory evaluation: in each case the serum thyrotropin (TSH), free thyroxine (FT4) and free triiodothyronine (FT3) where measured and confirmed the diagnosis. All the hormonal assays were performed with an ELISA method, and a routine hospital biochemical analyzer Modular E-170 by Roche was used for all the measurements, except leptin. Serum levels of leptin were determined in the Department of Clinical Biochemistry of the Poznań University of Medical Sciences using a commercial ELISA kit (R&D Systems Inc., MN, USA; microplater reader Sunrise Tekan, Switzerland), and were expressed as picograms per milliliter. Leptin was measured according to the manufacturer's recommended protocol, with a sensitivity of 7.8 pg/mL. An intra-assay and inter-assay coefficients of variation were 4.87% and 5.97%, respectively.

Statistical analysis

Statistical analysis was performed with the STATISTICA software by Statsoft. All the parameters were compared between the groups with the Mann-Whitney test. The correlations between FT4, FT3, TSH and leptin levels were calculated with the Spearman's correlation test. The values are given as the mean ± SD.

The study was conducted in accordance with the guidelines in The Declaration of Helsinki and was approved by the ethics committee of the Poznań University of Medical Sciences. All subjects gave informed consent to participate.

RESULTS

The clinical data of the hypothyroid and control subjects are shown in Table 1. The study groups were of similar age, and their body mass indices and waist and hip circumferences did not differ. However, as expected, the hypothyroid subjects showed higher levels of TSH and lower FT3 and FT4. Their plasma glucose did not differ. Serum leptin concentrations did not differ, either, p=0.09.

Table 1. Characteristics of hypothyroid subjects and euthyroid controls.

	SUBJECTS	CONTROLS	p-value
Sample size	22	22	
Age (years)	49.86±15.03, 52.50	43.73±10.14, 44.00	0.0723
BMI (kg/m^2)	28.05±6.39, 26.95	25.00±5.30, 23.20	0.0671
Waist circumf. (cm)	86.64±13.44, 84.50	82.05±12.80, 77.50	0.1620
Hip circumf. (cm)	100.95±8.95, 100.50	101.23±9.61, 100.00	0.9531
Plasma glucose	4.76±0.47, 4.55	4.99±0.80, 4.85	0.6380
FT4 (pmol/L)	2.65±2.19, 2.10	17.26±1.96, 17.10	0.0000
FT3 (pmol/L)	1.53±1.00, 1.43	4.57±0.61, 4.70	0.0000
TSH (pmol/L)	91.66±58.59, 81.35	1.75±0.84, 1.68	0.0000
Leptin (pg/mL)	18761.64±16973.96, 11296.50	18729.19±18014.05, 13268.50	0.9066

All values are shown as mean ± standard deviation, and median. Data were compared with Mann-Whitney test. $p<0.05$ denotes statistically significant.The abbreviation BMI stands for body mass index, circumf. for circumference, FT4 for plasma free thyroxine, FT3 for plasma free triiodothyronine, TSH for plasma thyrotropin.

To investigate the influence of thyroid status on the serum concentrations of leptin, correlations between leptin levels and FT3, FT4 and TSH were estimated separately in both study groups. In the hypothyroid subjects, those values did not correlate and the results for correlations were as follows: r=0.1039 and p=0.6453, r=0.0113 and p=0.9602, and r=–0.0525 and p=0.8165 for leptin and FT4, leptin and FT3, and leptin and TSH, respectively. The data are shown in Figure 1. Similarly, the following results were obtained in controls: r=–0.00056 and p=0.9980, r=0.248727 and p=0.2643, and r=–0.046919 and p=0.8357 for leptin and FT4, leptin and FT3, and leptin and TSH, respectively. These correlations are depicted in Figure 2.

DISCUSSION

Thyroid status markedly influences body weight and food intake. Thus, in a large number of hyperthyroid patients (85%) there is a decrease in body weight, whereas in 59% of hypothyroid patients there is an increase. (Ingbar, 1985). These changes in body weight are not due to changes in food intake; on the contrary, appetite is increased in 65% of hyperthyroid patients and decreased in 45% of hypothyroid patients. Under these circumstances, interactions between the thyroid status and fat tissue metabolism seem to be an important clinical issue. Since leptin is one of adipocyte-derived peptides and reflects the amount of fat tissue in the body, in this clini-

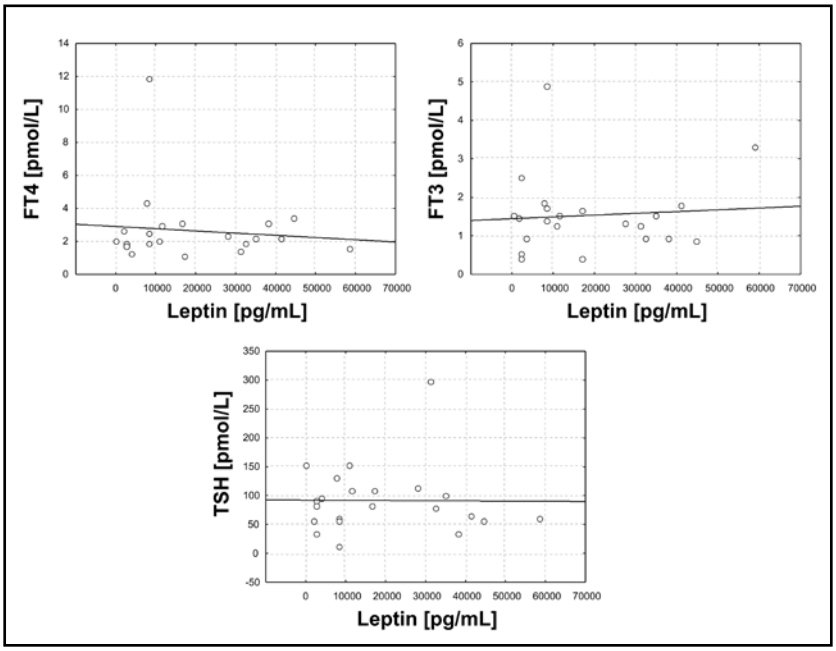

Figure 1. Correlations between circulating leptin levels and thyroid function in hypothyroid subjects. FT4 stands for serum free thyroxine, FT3 - serum free triiodothyronine, TSH - serum thyrotropin.

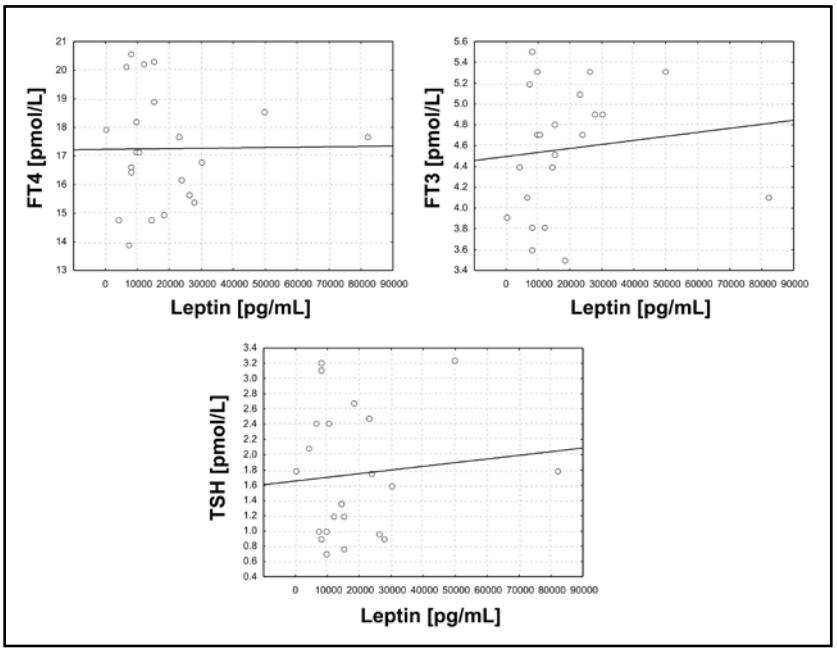

Figure 2. Correlations between circulating leptin levels and thyroid function in euthyroid subjects. FT4 stands for serum free thyroxine, FT3 - serum free triiodothyronine, TSH - serum thyrotropin.

cal study we analyzed the associations between plasma leptin levels and severe hypothyroidism in women *in vivo*. As controls, the same number of healthy euthyroid female subjects participated. Both subjects and controls where age-matched and had similar anthropometric parameters. In this setting, we were able to compare two identical groups of women, in whom a complete lack of thyroid function was the only differentiating factor. As a consequence, we examined the influence of hypothyroidism on the circulating plasma leptin levels *in vivo*.

As shown here, no interferences between the thyroid function and plasma leptin levels were found. Although circulating leptin has been thoroughly studied in various clinical conditions, and though a lot of extensive data on its function in human or animal metabolism exist, so far studies of serum leptin during abnormal thyroid function have shown conflicting results. Most studies of hyperthyroid patients have demonstrated similar leptin levels to those of euthyroid controls matched for sex, age and BMI (Corbetta *et al*. 1997; Leonhardt *et al*. 1998; Sreenan *et al*. 1997; Valcavi *et al*. 1997; Yoshida *et al*. 1998). Leptin values in hypothyroidism have been reported as being unchanged (Corbetta 1997, Sreenan *et al*. 1997), elevated (Leonhardt *et al*. 1998; Pinkney *et al*. 1998), or even decreased (Valcavi *et al*. 1997; Yoshida *et al*. 1998).

Moreover, patients with a leptin receptor mutation have been reported to be hypothyroid with lower levels of FT4 and delayed TSH response to TRH (Clement *et al*. 1998). Slightly elevated TSH levels have also been reported in leptin deficient children (Montague *et al*. 1997). In addition, obese subjects have slightly increased TSH levels; according to some authors, the elevation of TSH represents a secondary homeostatic adjustment for excessive adiposity. (Pinkney *et al*. 1998)

The controversies over leptin and thyroid hormone interactions may be due probably to many still unanswered questions regarding the molecular mechanisms which govern various metabolic pathways. One of the possible links between thyroid hormones and leptin might be mitochondrial uncoupling protein 3 (UCP3), a protein expressed in muscle and brown adipose tissue. UCP3 is regulated by both leptin and thyroid hormone. UCP3 levels have been reported to be decreased in hypothyroidism and increased in hyperthyroidism in animals (Gong *et al*. 1997).

The discrepancies of the above studies were due probably to limited number of cases or as a result of cross-sectional sampling with different groups of patients; in some of them the duration of study may have also played some role owing to natural fluctuations of thyroid hormones over time. To avoid it, we investigated two identical groups of women, by means of a cross-sectional comparison, and in addition, by a separate analysis of thyroid hormone-leptin interactions in each group. Similarly, a cross-sectional design was used previously be Yoshida *et al*. (1998), but these authors showed that serum leptin levels in hypothyroid patients were significantly lower than those in hyperthyroid patients and normal controls after adjusting for age, body weight and BMI. In our study, we achieved contrary results. There was no apparent explanation for this phenomenon, except some unknown inter-population variabilities.

In addition, some previous studies showed also a correlation between leptin levels and TSH in euthyroid subjects with a suggestion that activity of the pitutiary-thyroid axis is related to plasma leptin levels in both euthyroid and dysthyroid subjects, and the possibility of a functional link between these two endocrine axes

(Pinkney *et al*. 1998). Nonetheless, we do not demonstrate this correlation in neither group, and moreover, we do not show any correlations with respect to FT4 and FT3. Thus, since free thyroid hormones are a direct measure of thyroid function, and TSH an indirect one, neither the pituitary – thyroid axis, nor the thyroid *per se* influence circulating leptin levels. Under these circumstances, the previously presented possibility that TSH might be a potent suppressor of leptin gene expression should be questioned (Mantzoros *et al*. 1996).

We conclude that short-term hypothyroidism does not alter serum leptin concentrations and that no correlations between thyroid hormones and circulating levels exist.

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