Association of Hyperthyroidism With Serum Leptin Levels

Tomoatsu Nakamura, Shoichiro Nagasaka, San-e Ishikawa, Hiroko Hayashi, Takako Saito, Ikuyo Kusaka, Minori Higashiyama, and Toshikazu Saito

The present study was undertaken to determine whether thyroid hormones affect serum leptin levels in patients with hyperthyroidism. In 32 female patients with hyperthyroidism and 30 body mass index (BMI)-matched control subjects, there was no difference in serum leptin concentrations (9.0 ± 1.0 *v* 8.2 ± 0.9 μg/L). The serum leptin levels were compared with the expected values for serum leptin derived from the corresponding BMI with the formula for the control subjects (serum leptin [micrograms per liter] = 0.976 × BMI [kilograms per square meter] − 11.933, $P < .001$) and are expressed as the percent deviation (%leptin). There was a weak but significant positive correlation between serum free thyroxine (T_4) levels and %leptin in the combined analysis of patients with hyperthyroidism and control subjects ($r = .28$, $P < .05$). Multiple regression analysis also revealed the independent contribution of free T_4 levels to serum leptin. Antithyroid therapy ameliorated the hyperthyroidism and increased the BMI by 7.8% and the percent body fat by 9.9% in a subgroup of 21 patients with hyperthyroidism. However, serum leptin levels did not change during the 2-month therapeutic period (from 9.8 ± 1.4 to 8.7 ± 1.0 μg/L), and accordingly, %leptin significantly decreased from 133% ± 16% to 98% ± 11% ($P < .05$). A total of 6 months of observation in 12 hyperthyroid patients showed the same alterations in the anthropometric indexes, serum leptin, and %leptin. These results indicate that serum leptin is slightly increased in subjects with moderate hyperthyroidism, possibly due to the direct action of thyroid hormone, and the levels decline in accordance with the attainment of euthyroidism.

LEPTIN, the obese (ob) gene product in adipose tissue, is a hormone consisting of 167 amino acids that inhibits food intake and increases energy expenditure in rodents.[1,2] In humans, serum leptin levels are widely scattered and correlate with the body mass index (BMI) and body fat, and there is some evidence for a physiologic role of leptin in food intake and energy expenditure.[3] The expression of leptin mRNA is increased by insulin,[4] glucocorticoids,[5] and several cytokines such as tumor necrosis factor alpha and interleukin-1.[6] Also, serum leptin levels are elevated in some pathologic disorders, including chronic renal failure,[7] acute sepsis,[8] and diabetic ketoacidosis.[9] In contrast, fasting solely reduces serum leptin levels.[10]

Thyroid hormones have a permissive effect on adaptive thermogenesis and promote the activity of the adrenergic receptor system.[11] A decrease in body weight is commonly found in patients with hyperthyroidism, and it is also linked to a reduction in body fat. There are several reports showing no alteration in serum leptin levels in thyroid dysfunction,[12-14] although a few reports noted a decrease in serum leptin in hypothyroidism.[15,16] Yoshida et al[17] demonstrated that thyroid hormone increases the expression of leptin mRNA and secretion of leptin in in vitro adipocytes. Serum leptin concentrations were increased[18,19] or unchanged[12-16,20,21] in patients with hyperthyroidism, but the reason for this variability is unknown.

In the present study, we determined whether thyroid hormone affects serum leptin levels in a larger number of subjects with endogenous hyperthyroidism. Also, the effect of the antithyroid therapy on serum leptin levels was studied.

SUBJECTS AND METHODS

Subjects

Thirty-two patients with newly diagnosed hyperthyroidism were examined between November 1997 and June 1999. They were all females aged 41 ± 3 years (mean ± SEM; range, 17 to 72) with a BMI of 19.9 ± 0.4 kg/m^2 (Table 1). They lost 4.3 ± 0.8 kg body weight during the past year. Subjects with liver and renal dysfunction and diabetes mellitus were excluded. Blood collections were made at 8 AM after an overnight fast, before the start of the antithyroid therapy. All subjects were treated with methimazole only during the observation period. Blood samples were analyzed for serum leptin, free triiodothyronine (T_3), free thyroxine (T_4), thyrotropin (TSH), and TSH receptor antibody. Height, body weight, and percent body fat were determined at the same time. Thirty age- and BMI-matched females served as control subjects (Table 1). The number of postmenopausal females was identical between these 2 groups, and none of the postmenopausal women had used hormone replacement therapy.

Twenty-one of the 32 patients were evaluated 1 and 2 months after the start of therapy. Furthermore, 12 of the 21 patients were also investigated 6 months later. The protocol was approved by the ethics committee of Jichi Medical School, and all subjects provided informed consent for the study.

Measurements

Serum leptin levels were measured by radioimmunoassay using leptin radioimmunoassay kits (Linco Research, St. Charles, MO). The intraassay and interassay coefficients of variation were less than 5%. Free T_3, free T_4, and TSH levels were measured by radioimmunoassay using a free T_3 radioimmunoassay kit, free T_4 radioimmunoassay kit (Ortho-Clinical Diagnosis, Tokyo, Japan), and TSH radioimmunoassay kit (Dainabott, Tokyo, Japan), respectively. TSH receptor antibody was determined by radioreceptor assay (Cosmic, Tokyo, Japan). Body weight and percent body fat were measured with a bioelectrical impedance analyzer (TBF-305; Tanita, Tokyo, Japan).

Statistical Analysis

All data are presented as the mean ± SEM. Simple linear regression analysis was performed to calculate correlations. Student's unpaired or paired *t* test, nonparametric 2-way ANOVA, or the χ^2 test were used

From the Division of Endocrinology and Metabolism, Department of Medicine, Jichi Medical School, Tochigi, Japan.

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Address reprint requests to Tomoatsu Nakamura, MD, Division of Endocrinology and Metabolism, Department of Medicine, Jichi Medical School, 3311-1 Yakushiji, Minamikawachi, Tochigi 329-0498, Japan.

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Table 1. Clinical and Biochemical Characteristics of the Patients With Hyperthyroidism and Control Subjects

Characteristic	Control	Patients With Hyperthyroidism	P*
No. of subjects	30	32	—
Age, yr (range)	48 ± 3 (20-80)	41 ± 3 (17-72)	NS
Postmenopausal (n)	9	10	NS
BMI (kg/m²)	20.6 ± 0.5	19.9 ± 0.4	NS
Serum TSH (mU/L)	—	<0.02	—
Serum free T_4 (pmol/L)	14.9 ± 0.5	77.3 ± 9.6	<.0001
Serum free T_3 (pmol/L)	—	31.4 ± 6.0	—
Serum leptin (μg/L)	8.2 ± 0.9	9.0 ± 1.0	NS
% leptin	102 ± 9	122 ± 11	NS

Abbreviation: NS, not significant.

*Determined by Student's unpaired *t* test, except for postmenopausal (χ^2 test).

appropriately to compare differences. Multiple regression analysis was used to evaluate determinants of the serum leptin level. The statistical package StatView (Abacus Concepts, Berkeley, CA) for Macintosh Version 4.5 was used for the analyses. A *P* value less than .05 was considered significant.

RESULTS

In 32 patients with hyperthyroidism, serum free T_4 was 77.3 ± 9.6 pmol/L, free T_3 was 31.4 ± 6.0 pmol/L, and TSH was less than 0.02 mU/L, respectively. Twenty-eight of the 32 patients had a positive TSH receptor antibody level of 40% ± 5% (normal, <15%). There was no difference in serum leptin concentrations between patients with hyperthyroidism and control subjects (Table 1). Before the treatment, there was a positive correlation between the serum leptin level and BMI in patients with hyperthyroidism (Fig 1A), but the correlation was stronger in control subjects (Fig 1B; serum leptin [micrograms per liter] = 0.976 × BMI [kilograms per square meter] − 11.933). Serum leptin values were compared with the expected levels for serum leptin derived from the corresponding BMI with the above formula for the control subjects, and are expressed as the percent deviation (%leptin). There was a weak but significant positive correlation between serum free T_4 and %leptin in the combined analysis of patients with hyperthyroidism and control subjects (Fig 2). Multiple regression analysis showed the independent contribution of serum free T_4, along with the BMI, to serum leptin concentrations (Table 2).

Table 3 shows anthropometric parameters and serum TSH, free T_4, and leptin levels during 2 months of antithyroid therapy in the 21 patients with hyperthyroidism. In accordance with the amelioration of thyrotoxicosis, the body weight, BMI, percent body fat, and fat mass significantly increased by 7.4%, 7.8%, 9.9%, and 17.4%, respectively. Serum leptin levels remained unchanged despite the increase in the anthropometric indexes, and accordingly, %leptin was significantly decreased. After 6 months of therapy in the 12 patients, the same alterations in the anthropometric indexes, serum leptin, and %leptin were observed (Table 4). The correlation coefficient between the serum leptin level and BMI in hyperthyroid patients increased to .454 (n = 21, *P* = .058) after 2 months of antithyroid therapy.

DISCUSSION

In normal subjects, serum leptin levels are widely scattered and correlate with the BMI and body fat. Serum leptin levels are higher in females versus males with the same BMI.[22] There is a considerable variability in leptin levels at each BMI, suggesting that some unknown hormonal, genetic, and/or environmental factors may be involved in the determinants of serum leptin concentrations. In the present study, serum leptin in patients with hyperthyroidism showed a weaker correlation with the BMI than that in the normal subjects. There is moderate disagreement about serum leptin levels in patients with thyrotoxicosis: some studies show increased levels of serum leptin,[18,19] but others show unchanged levels.[12-16,20,21] The reason for these discrepant results is unknown. In the present study, we show that serum free T_4 levels are positively correlated with %leptin and also contribute to serum leptin in the multiple regression analysis. The %leptin was also significantly decreased in accordance with the amelioration of hyperthyroidism after 2 or 6 months of the observation period. These findings suggest that an excess of thyroid hormone per se may contribute to the alteration in serum leptin levels, in addition to the BMI, in patients with hyperthyroidism.

The following possible explanations apply to the increase in

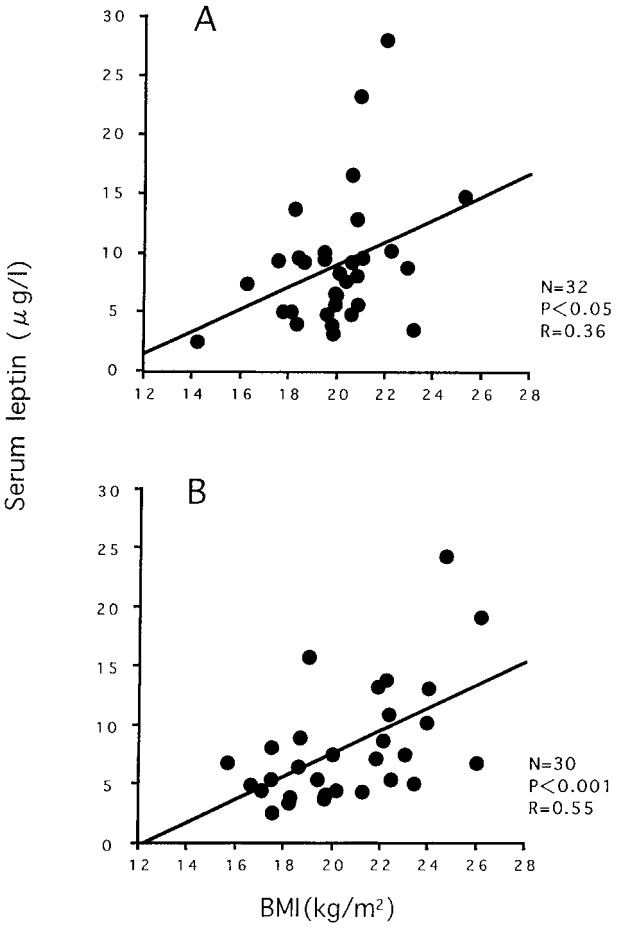

Fig 1. Relationship between the BMI and serum leptin in patients with hyperthyroidism before treatment (A) and control subjects (B).

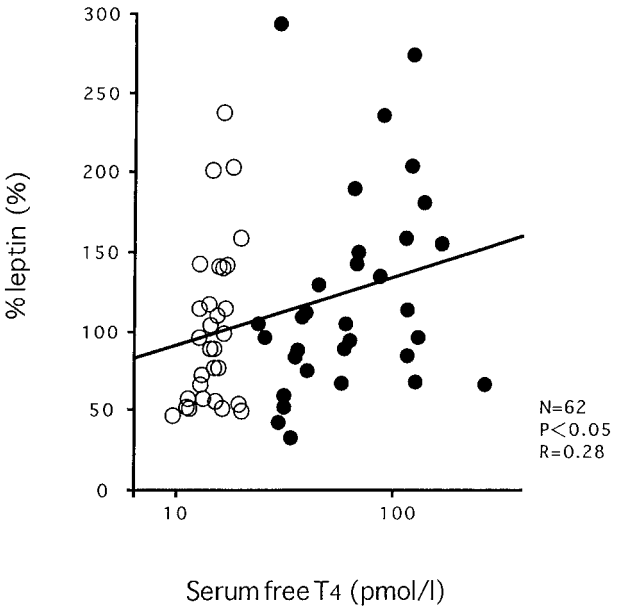

Fig 2. Relationship between serum free T_4 and %leptin in the combined analysis of patients with hyperthyroidism (●, n = 32) and control subjects (○, n = 30). Note that serum free T_4 concentrations were logarithmically transformed because of the skewed deviation.

serum leptin in hyperthyroidism. First, Yoshida et al[17] reported that T_3 dose-dependently increases the expression of leptin mRNA in cultured 3T3-L1 adipocytes and the secretion of leptin in conditioned media. Therefore, it seems likely that the degree of thyrotoxicosis has a considerable effect on serum leptin in clinical settings. In fact, the degree of hyperthyroidism tended to be more severe in the studies reporting increased leptin levels,[18] including ours. Since thyrotoxicosis also activates the adrenergic receptor system and the system downregulates leptin mRNA expression in adipocytes,[5] the effect of thyroid hormone excess may be obscure in cases of mild hyperthyroidism. Second, several cytokines such as tumor necrosis factor alpha and interleukin-1 are known to upregulate leptin mRNA expression.[6] As increased concentrations of serum tumor necrosis factor alpha have been reported in patients with Graves' disease,[23] such inflammatory cytokines might participate in the increase in serum leptin. Third, since adipose tissue has receptors for TSH,[24] TSH receptor antibody may cross-react with TSH receptors in adipose tissue to affect leptin secretion. However, this scenario is less likely, since we found no correlation between the levels of TSH receptor antibody and serum leptin (data not shown). Moreover, there is little evidence that TSH is involved in the regulation of leptin secretion. Finally, it may be hypothesized that an excess of thyroid hormone causes a resistance to leptin's action, and this indirectly increases circulating leptin levels. This hypothesis resembles leptin resistance in obesity, but requires further investigation.

Table 2. Multiple Regression Analysis for Serum Leptin (log-transformed) as a Dependent Variable

Parameter	Regression Coefficient	SE	*P*
Intercept	−.363	0.286	.209
BMI (kg/m²)	.051	0.011	<.001
Serum free T_4 (pmol/L)	.161	0.075	.036
Age (yr)	−.001	0.002	.561

NOTE. R^2 = .284.
Abbreviation: SE, standard error of parameter estimate.

Table 3. Clinical Course of 21 Patients With Hyperthyroidism During Two Months of Antithyroid Therapy

Parameter	Before Treatment	After Treatment		*P**
		1 mo	2 mo	
Body weight (kg)	47.9 ± 1.0	49.8 ± 1.0	51.3 ± 1.0	<.0001
BMI (kg/m²)	19.8 ± 0.3	20.7 ± 0.2	21.3 ± 0.3	<.0001
Body fat (%)	25.8 ± 1.2	27.1 ± 1.2	28.2 ± 1.2	<.001
Fat mass (kg)	12.8 ± 0.8	14.0 ± 0.9	14.8 ± 0.8	<.0005
Serum TSH (mU/L)	<0.02	0.3 ± 0.2	2.5 ± 1.8	<.0001
Serum free T_4 (pmol/L)	76.8 ± 10.4	27.2 ± 3.9	14.2 ± 1.9	<.0001
Serum leptin (μg/L)	9.8 ± 1.4	9.1 ± 1.1	8.7 ± 1.0	NS
%leptin	133 ± 16	111 ± 14	98 ± 11	<.05

Abbreviation: NS, not significant.
*Determined by nonparametric 2-way ANOVA.

The prediction of body fat by the bioelectrical impedance method is influenced by the percent body water. An expansion of extracellular water, which could enhance biologic impedance, apparently overestimates body fat. In the hyperthyroid state, the extracellular water level is elevated compared with that in normal subjects.[25] Therefore, percent body fat might be overestimated in the hyperthyroid patients before the therapy, and the increment in percent body fat during therapy might be underestimated. This consideration would further support our conclusion.

In summary, serum leptin levels were slightly increased in subjects with moderate hyperthyroidism, possibly due to the direct action of thyroid hormone, and the levels declined in accordance with the attainment of euthyroidism. To further strengthen these findings, it would be mandatory to study a larger number of patients with more severe hyperthyroidism. The changes in circulating leptin levels may modulate alterations in energy expenditure during the therapeutic course of hyperthyroidism, but further study is necessary to elucidate the exact interactions among thyroid hormones, leptin, and energy expenditure.

Table 4. Clinical Course of 12 Patients With Hyperthyroidism During Six Months of Antithyroid Therapy

Parameter	Before Treatment	Six Months After Treatment	*P**
Body weight (kg)	48.2 ± 1.2	53.5 ± 1.5	<.0001
BMI (kg/m²)	19.5 ± 0.4	21.8 ± 0.4	<.0001
Body fat (%)	26.8 ± 1.8	28.9 ± 1.7	<.01
Fat mass (kg)	13.6 ± 1.3	15.5 ± 1.2	<.05
Serum TSH (mU/L)	<0.02	2.6 ± 0.8	<.0001
Serum free T_4 (pmol/L)	68.5 ± 9.8	14.5 ± 1.9	<.0001
Serum leptin (μg/L)	8.5 ± 1.1	8.7 ± 1.2	NS
%leptin	122 ± 17	90 ± 11	<.01

Abbreviation: NS, not significant.
*Determined by Student's paired *t* test.

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