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Change of visfatin, C-reactive protein concentrations, and insulin sensitivity in patients with hyperthyroidism

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Abstract

The present study was undertaken to evaluate the change of circulating visfatin, C-reactive protein (CRP) concentrations, and insulin sensitivity in patients with hyperthyroidism. We studied 19 adult patients (14 women and 5 men aged 32.6 ± 1.8 years) with hyperthyroidism due to Graves disease and 19 age- and sex-matched euthyroid controls (17 women and 2 men aged 36.7 ± 2.7 years). All hyperthyroid patients were treated with 1 of 2 antithyroid drugs and were reevaluated after thyroid function normalized. Before antithyroid treatment, the hyperthyroid group had significantly higher visfatin plasma concentration (mean ± standard error of the mean, 20.7 ± 1.8 ng/mL) than the control group (16.2 ± 1.3 ng/mL, $P = .044$); but the visfatin level dropped significantly after treatment (12.0 ± 1.4 ng/mL, $P < .001$). The reciprocal index of homeostasis model assessment of insulin resistance (HOMA–IR) in the hyperthyroid group was higher before treatment (2.06 ± 0.26 mmol mU/L*L) than after treatment (1.21 ± 0.16 mmol mU/L*L, $P = .027$). There was no significant difference in serum glucose, high-sensitivity CRP, and insulin levels between hyperthyroid and control groups and in the hyperthyroid group before and after treatment. Body mass index–adjusted visfatin levels were significantly elevated in the hyperthyroid group. Pearson correlation revealed that visfatin, glucose, insulin, and HOMA-IR values positively correlated with triiodothyronine and free thyroxine levels. However, visfatin did not correlate with insulin and HOMA-IR levels. The results indicated that plasma visfatin concentration was elevated in hyperthyroidism due to Graves disease, but serum CRP levels were not. Plasma visfatin levels were not associated with indicators of insulin resistance in hyperthyroid patients.

1. Introduction

Hyperthyroidism has been linked to reduced lean and fat body mass, resulting in lower-than-normal body weight. Patients with hyperthyroidism often have disrupted intermediary metabolism and thyrotoxicosis that has been associated with insulin resistance [1-3]. Abnormal levels of adipocytokines (eg, leptin, adiponectin, and resistin) in patients with thyroid dysfunction have been reported [4-7]. Visfatin, an adipose tissue–derived protein, is known to have insulin-like metabolic effects [8]. The molecule was previously identified as a growth factor for early B-lymphocytes and named as *pre-B cell colony-enhancing factor* [9]. The gene for visfatin is expressed and regulated in adipocytes [10,11]. Visfatin gene expression in visceral fat is increased in obese subjects, and the plasma concentration of visfatin has been associated more strongly with the amount of visceral fat than subcutaneous fat [8].

The plasma levels of visfatin in patients with hyperthyroidism due to Graves disease have not been studied. The insulin-like effects of visfatin, such as stimulating glucose transport into muscle cells and adipocytes and inhibiting glucose production in hepatocytes, are dependent on the plasma concentration [8]. Intravenous injection of recombinant visfatin in mice decreases plasma glucose in a dose-dependent fashion [8]. Visfatin appears to play a role in

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glucose homeostasis and may contribute to the pathogenesis of insulin resistance in hyperthyroidism. In addition, proinflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor–α (TNF-α) are elevated in Graves disease [12-14], which may affect insulin sensitivity and interact with visfatin.

The objective of this study was to compare plasma visfatin concentrations in subjects with hyperthyroidism due to Graves disease before and after antithyroid treatment and in euthyoid control subjects. The relationships among visfatin, serum inflammatory marker C-reactive protein (CRP), insulin concentrations, and homeostasis model assessment of insulin resistance index (HOMA-IR) were evaluated.

2. Materials and methods

2.1. Subjects

The study enrolled 19 patients with hyperthyroidism due to Graves disease (14 women and 5 men) and 19 age- and sex-matched euthyroid controls (17 women and 2 men). The diagnosis of Graves disease was made by the presence of circulating thyrotropin receptor antibody (TRAB) in patients with hyperthyroidism. Informed consents were obtained from all subjects after thorough explanation of the procedures. All subjects were free of diabetes mellitus and hypertension. Of the 19 hyperthyroid patients, 8 were treated with propylthiouracil (Procil; Nysco, Taipei, Taiwan) and 11 with carbimazole (Neo-Thyreostat; Dr Herbrand, Gengenbach, Germany). Thyroid function was normalized after 3 to 7 months of treatment (mean = 5.4 ± 0.4 months). The patients were evaluated at the time of diagnosis and after thyroid function normalized.

All subjects received physical examination (height and weight). Samples of venous blood were obtained from an antecubital vein after overnight fast. Blood samples were centrifuged immediately, and the serum or plasma was stored at −20°C until assayed. The plasma and serum samples were tested to measure serum concentrations of free thyroxine (FT4), total triiodothyronine (T3), thyrotropin (TSH), glucose, insulin, high-sensitivity (HS)–CRP, and plasma concentrations of visfatin, all after overnight fasting. Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters. Insulin resistance was estimated by using the HOMA-IR index, calculated as serum glucose concentration (in millimoles per liter) × serum insulin concentration (in microunits per liter)/22.5 [15].

2.2. Biochemistry and hormone analyses

Serum FT4, T3, TSH, insulin, and HS-CRP concentrations were measured using chemiluminescent immunoassays (Immulite 2000; Diagnostic Products, Los Angeles, CA). The intraassay and interassay coefficients of variation were 5.8% and 6.7%, respectively, for FT4 levels; 7.6% and 8.6% for T3 levels; 6.2% and 10.0% for TSH levels; 4.0% and 4.9% for insulin levels; and 4.7% and 7.1% for HS-CRP levels. The sensitivity of the assays was 0.15 ng/dL for FT4, 19 ng/dL for T3, 0.002 μIU/mL for TSH, 2 μIU/mL for insulin, and 0.01 mg/dL for HS-CRP. The reference range was 0.8 to 1.9 ng/dL for FT4, 84 to 172 ng/dL for T3, 0.4 to 4 μIU/mL for TSH, 5 to 25 μIU/mL for insulin, and 0.01 to 50 mg/dL for HS-CRP.

Plasma visfatin concentration was measured using the "competitive" enzyme immunoassay (Phoenix Pharmaceuticals, Belmont, CA). The intraassay and interassay coefficients of variation were 10.0% and 7.3%, respectively. The sensitivity of the assay was 3.07 ng/mL. The range was 0.1 to 1000 ng/mL. The linear range was 3.07 to 54 ng/mL.

2.3. Statistical analyses

Data were reported as mean ± standard error of the mean (SEM). Comparisons of hyperthyroid subjects before treatment, hyperthyroid subjects after treatment, and euthyroid control subjects were made by using 1-way analysis of variance (ANOVA) and Bonferroni test for post hoc multiple comparisons. Mann-Whitney test was used for nonparametric data. Correlations between parameters were assessed by using Pearson correlation analysis. A value of $P < .05$ was considered as statistically significant.

3. Results

The demographic and clinical characteristics of the study population are shown in Table 1. The mean ± SEM age was 32.6 ± 1.8 years for hyperthyroid subjects and 36.7 ± 2.7 years for matching control subjects. As expected, subjects in the hyperthyroid group before treatment had lower TSH and higher T3 and FT4 serum concentrations than they did after

Table 1
Characteristics of control subjects and hyperthyroid subjects before and after treatment

	Control (n = 19)	Hyperthyroid (n = 19)	
		Pretreatment	Posttreatment
Age (y)	36.7 ± 2.7	32.6 ± 1.8	–
Sex (F/M)	17/2	14/5	–
Postmenopause	3/17	2/14	–
Body weight (kg)	55.4 ± 1.9	53.9 ± 1.8	55.6 ± 2.0
BMI (kg/m^2)*	22.9 ± 0.8	20.6 ± 0.5	21.1 ± 0.6
Free T4 (ng/dL)*	1.35 ± 0.05	5.22 ± 0.53	1.14 ± 0.09
T3 (ng/dL)*	113.1 ± 5.3	476.0 ± 46.9	115.6 ± 8.0
TSH (μIU/mL)*	1.32 ± 0.05	0.02 ± 0.00	3.47 ± 1.65
Glucose (mmol/L)	4.93 ± 0.10	5.14 ± 0.08	4.79 ± 0.12
Visfatin (ng/L)*	16.2 ± 1.3	20.7 ± 1.8	12.0 ± 1.4
Insulin (μIU/mL)	7.80 ± 1.06	8.86 ± 1.02	5.66 ± 0.69
HOMA-IR (mmol mU/L*L)*	1.71 ± 0.23	2.06 ± 0.26	1.21 ± 0.16
HS-CRP (mg/dL)	0.10 ± 0.03	0.14 ± 0.05	0.04 ± 0.01
TRAB (%)*	-	44.9 ± 5.7	29.1 ± 5.0

Data are means ± SEM. Comparisons among 3 groups were made by 1-way ANOVA. *$P < .05$. Post hoc test by Bonferroni. Visfatin: control vs pretreatment, $P = .044$; pretreatment vs posttreatment, $P < .001$. HOMA-IR: pretreatment vs posttreatment, $P = .027$.

treatment or the control group. The hyperthyroid group before treatment also had higher visfatin plasma concentrations (20.7 ± 1.8 ng/mL) than they did after treatment (12.0 ± 1.4 ng/mL, $P = .044$) and the control group (16.2 ± 1.3 ng/mL, $P < .001$). In addition, HOMA-IR values were higher in the hyperthyroid group before treatment (2.06 ± 0.26 mmol mU/L*L) than after treatment (1.21 ± 0.16 mmol mU/L*L, $P = .027$). There was no significant difference in serum glucose, HS-CRP, and insulin levels between the hyperthyroid and control groups and in the hyperthyroid group before and after treatment.

Body mass index–adjusted visfatin levels were higher in the hyperthyroid group before treatment than the group after treatment as well as the control group ($P < .001$ compared with control and $P = .024$ compared with the same group after treatment, respectively) (Table 2). In addition, BMI-adjusted insulin levels and HOMA-IR values were significantly higher in the hyperthyroid group before treatment. The BMI-adjusted HS-CRP levels were not significantly different.

Changes in plasma visfatin concentrations after antithyroid drug therapy were compared between patients who took propylthiouracil and those who took carbimazole. The plasma visfatin concentrations decreased by 8.2 ± 3.8 ng/mL in the 8 patients receiving propylthiouracil and decreased by 9.3 ± 2.8 ng/mL in the 11 patients receiving carbimazole. The difference between these 2 drugs was not significantly different.

Correlation analyses performed in the patients with hyperthyroidism (Table 3) showed that visfatin, glucose, insulin, and HOMA-IR values correlated with thyroid hormone levels (T3, FT4), but not with BMI. None of these parameters correlated with HS-CRP. Visfatin levels did not correlate with insulin levels and HOMA-IR values. Insulin, but not visfatin, correlated with glucose levels.

4. Discussion

Adipocytokines play a crucial role in the regulation of energy homeostasis, insulin sensitivity, lipid and carbohydrate metabolism, and inflammatory and atherogenic reactions [16-22]. The adipocytokine visfatin has metabolic effects quantitatively similar to those of insulin [8]. However, the relationship between visfatin and insulin resistance remains inconclusive. One study assessed the association between serum visfatin concentrations and levels of inflammatory markers (IL-6 and CRP) and insulin-resistance (HOMA-IR). The results showed that circulating visfatin levels were correlated with serum levels of IL-6 and CRP, but not with HOMA-IR [23], indicating that circulating visfatin levels may reflect the body's inflammation status rather than insulin sensitivity.

In this study, we showed elevated plasma visfatin and BMI-adjusted visfatin levels in patients with hyperthyroidism, which decreased after antithyroid treatment. In addition, visfatin also correlated with thyroid hormones including T3 and FT4. The high concentration of visfatin in these patients with hyperthyroidism may reflect a state of visfatin resistance.

The direct effects of hyperthyroidism on plasma adipocytokines concentrations have not been well understood. Patients with Graves disease have elevated proinflammatory cytokines such as IL-6 and TNF-α [12-14]. The indirect stimulation by these proinflammatory factors may lead to generalized metabolic consequences. In our study, hyperthyroidism was associated with elevated plasma visfatin levels but not serum CRP levels; and plasma visfatin and thyroid hormones (T3 and FT4) levels were positively correlated in patients with Graves disease hyperthyroidism. We found no correlations between plasma visfatin and serum CRP levels.

Patients with hyperthyroidism are known to have elevated fasting serum glucose levels [24,25], which may be explained by increased endogenous glucose production through more rapid glycogenolysis and gluconeogenesis [24,26,27]. The speed of insulin-stimulated glucose disposal in peripheral tissues is variable in hyperthyroidism and may be normal, increased, or decreased [3]. Although we found no significant difference in serum glucose concentration between the hyperthyroid and euthyroid groups, HOMA-IR values and BMI-adjusted insulin concentration were elevated in hyperthyroid patients. In

Table 2
Comparisons of BMI-adjusted plasma visfatin concentration, insulin concentration, and HOMA-IR value among the control and hyperthyroid groups before and after treatment

	Control (n = 19)	Hyperthyroid (n = 19)	
		Pretreatment	Posttreatment
Visfatin/BMI*	0.73 ± 0.06	1.02 ± 0.09	0.58 ± 0.07
HS-CRP/BMI	0.004 ± 0.001	0.007 ± 0.003	0.002 ± 0.001
Insulin/BMI*	0.33 ± 0.04	0.43 ± 0.05	0.26 ± 0.03
HOMA-IR/BMI*	0.07 ± 0.01	0.10 ± 0.01	0.06 ± 0.01

Data are means ± SEM. Comparisons among 3 groups were made by 1-way ANOVA. *$P < .05$. Post hoc test by Bonferroni. Visfatin/BMI: control vs pretreatment, $P = .000$; pretreatment vs posttreatment, $P = .024$. Insulin/BMI: pretreatment vs posttreatment, $P = .010$. HOMA-IR/BMI: pretreatment vs posttreatment, $P = .005$.

Table 3
Pearson correlation coefficients in patients with hyperthyroidism due to Graves disease

Factors	Visfatin	Glucose	Insulin	HOMA-IR	HS-CRP
BMI	−0.225	0.037	0.219	0.207	−0.78
T3	0.476**	0.360*	0.328*	0.364*	0.164
FT4	0.467**	0.411*	0.405*	0.444**	0.262
Visfatin	1	0.261	0.162	0.177	0.257
Insulin	0.162	0.386*	1	0.991**	0.213
HOMA-IR	0.177	0.493**	0.991**	1	0.202
HS-CRP	0.257	0.042	0.213	0.202	1
TRAB	0.366*	0.011	0.099	0.098	0.205

* $P < .05$.
** $P < .01$.

addition, HOMA-IR and BMI-adjusted insulin levels were positively correlated with T3 and FT4 levels in patients with Graves disease. These findings were consistent with the assumption that hyperthyroidism is associated with higher insulin resistance. However, the serum insulin and HOMA-IR levels did not correlate with plasma visfatin concentration. Unlike insulin, plasma visfatin was not correlated with serum glucose levels. Hence, visfatin may not indicate insulin resistance in hyperthyroidism.

In summary, plasma visfatin concentration was elevated in hyperthyroidism due to Graves disease; but serum CRP levels were not. Plasma visfatin levels were not associated with indicators of insulin resistance in hyperthyroid patients.

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