Visfatin plasma concentrations in patients with hyperthyroidism and hypothyroidism before and after control of thyroid function

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ABSTRACT. Alterations in thyroid function are associated with changes in body weight, metabolism, and low-grade inflammation. In several studies, plasma levels of visfatin were found to be associated with body mass index, diabetes, and metabolic syndrome. In our study we aimed to evaluate visfatin levels according to thyroid dysfunction. The study cohort comprised 56 Hashimoto thyroiditis patients with hypothyroidism (43.94±14.27 yr), 56 Graves patients with hyperthyroidism (45.87±13.28 yr), and 56 euthyroid healthy subjects (45.23±7.11 yr) as a control group. In addition, we evaluated the effect of therapy on plasma visfatin levels in 16 hyperthyroid and in 25 hyperthyroid patients. Markedly low visfatin levels were found in hyperthyroid patients [9.44 (8.07-10.8) ng/ml] compared with the hypothyroid [49.93 (40.72-59.1) ng/ml] and control groups [38.6 (30.6-46.6) ng/ml] (p<0.001, p<0.001). Plasma visfatin levels in patients with hypothyroidism decreased significantly following treatment [58.58 (10.21-190.7) ng/ml vs 40.00 (10.01-102.6) ng/ml; p=0.001]. Plasma visfatin levels increased significantly after antithyroid therapy in patients with hyperthyroidism [7.86 (1.02-19.23) ng/ml vs 12.63 (3.48-110.9) ng/ml; p<0.001]. There were negative correlations between visfatin levels with free T3 (r=-0.719, p<0.001), and free T4 (r=-0.716, p<0.001) levels. There was a positive correlation between visfatin and TSH levels (r=0.701, p<0.001). There was a negative correlation between delta visfatin levels with delta free T3, delta free T4 (r=-0.868, p<0.001; r=-0.624, p<0.001). Visfatin thus seems to be regulated by thyroid hormones. While the influence of thyroid dysfunction on adipocytokine production and release is still poorly understood, the results of our study suggest that the effects of hyper- and hypothyroidism on various metabolic parameters may be partly mediated by visfatin. (J. Endocrinol. Invest. 32: 435-439, 2009) ©2009, Editrice Kurtis

INTRODUCTION

Thyroid hormones are potent regulators of body metabolism. Hypothyroidism is usually associated with a modest weight gain and increased plasma concentrations of lipids whereas hyperthyroidism is related with weight loss and reduction of plasma lipids (1-3). Metabolic disturbances in carbohydrate metabolism are also frequent in patients with thyroid dysfunction (4). These patients have disordered appetite and food intake as well as changes in adipose tissue metabolism (3). Therefore, abnormal thyroid function may be associated with disturbances in the production of hormones produced by fat tissue. Visfatin is a novel adipokine that is predominantly secreted by visceral adipose tissue. Insulin-mimetic effects were documented for this new adipokine, which are mediated by direct binding and activation of the insulin receptor (5). However, the literature about visfatin’s physiology remains controversial. While circulating levels of visfatin were initially correlated with visceral fat mass and with central obesity (6), several studies have noted no difference in visfatin expression between visceral and subcutaneous adipose tissue (7, 8) and no correlation between circulating levels and measures of anthropometry and fat mass (7-10). As such, it is apparent that the physiological relationships of this adipokine remain unclear at this time (11).

It is reported that visfatin may play a role in cholesterol homeostasis (12). In humans, plasma visfatin is increased in disturbances of the carbohydrate metabolism as, for example, in Type 2 diabetes (6). It is increasingly evident from the literature that adipocytokines play a significant role in the induction of atherogenesis and dysregulated angiogenesis (10). Visfatin is also associated with low-grade inflammation and body mass index (BMI) (13). Further studies towards regulation of visfatin production in adipocytes showed that tumor necrosis factor-α and interleukin-6 (IL-6) decreased visfatin expression, whereas insulin did not alter the expression of visfatin. Thyroid status may effect cytokines that regulate visfatin secretion (14).

There is some evidence regarding the association between several adipocytokines and thyroid function (15, 16). Further, changes in thyroid hormone levels as seen in hyper/hypothyroidism and their correlations have been previously shown to alter adipokine secretion (17). Additional studies are needed to clarify the contribution of these adipose factors in normal thyroid function and endocrine function of adipose tissue. However, the potential relationship of new adipocytokines, such as visfatin, with thyroid dysfunction needs to be investigated (4). We hypothesized that hormones that affect normal adipose energy storage would also effect visfatin secretion. Recently, MacLaren et al. observed multiple roles of hor-
mones on visfatin expression and down regulation of visfatin expression by T3 (17).

The aim of the present work was therefore to evaluate the serum concentrations of visfatin in patients with hypothyroidism and hyperthyroidism both before therapy and after normalization of thyroid dysfunction with appropriate therapy.

MATERIALS AND METHODS

Subjects
The participants of the study were selected from patients referred to the Department of Endocrinology and Metabolism, Sutcuimam School of Medicine, Turkey. In the period between January 2007 and December 2007, 56 Hashimoto thyroiditis patients with hypothyroidism (43.94±14.27 yr, 45 females/11 males), 56 Graves patients with hyperthyroidism (45.87±13.28 yr, 44 females/12 males), and 56 euthyroid healthy subjects (45.23±7.11 yr, 41 females/15 males) as control group were consecutively enrolled in the study. Controls were initially admitted to the check-up policlinic to establish if they had goiter. Exclusion criteria for controls were thyroid or any other chronic disease. Healthy controls had no goiter or clinical evidence of thyroid disease or family history of any autoimmune disease. All patients were new admissions to our department. Patients with hypo/hyperthyroidism were newly diagnosed and previously untreated. Graves disease was diagnosed on the basis of clinical and laboratory evidence of hyperthyroidism and diffuse goiter and was supported by the presence of TSH receptor antibody, increased radioiodine uptake in thyroid scintigraphy, and/or exophthalmoses. Hashimoto thyroiditis was diagnosed by the presence of goiter, hypothyroidism, and elevated microsomal or thyroid peroxidase auto-antibodies. Thyroid ultrasound showed a reduced echogenicity. Exclusion criteria were sustained hypertension, heart failure, peripheral vascular disease, smoking, acute or chronic infections, cancer, hepatic or renal disease, and using insulin and antilipidemic medications. Patients with diabetes or chronic illnesses were also excluded from the study. Patients ultimately admitted to the study were not taking any drugs. The study plan was reviewed and approved by our institutional review committee, and informed consent was obtained from all patients and control subjects.

Study design
The study was devised to be partly cross-sectional and partly prospective. Blood samples were drawn from the brachial vein after 12 h overnight fasting, between 08:00 and 09:00 h. Hyperthyroid patients were treated with levothyroxine (L-T4) (Abdi Ibrahim Co., Istanbul, Turkey) starting from a dose of 50 μg/day. TSH was measured every 4-6 weeks to adjust L-T4 dose. Mean L-T4 dose required to restore euthyroidism was 100±25 μg/day. Re-evaluation was performed with venous blood sampling at least 4 months after restoration of euthyroidism. Hyperthyroid patients were treated with an initial dosage of propfanolon (40-60 mg/day) and propthyouracil (300-400 mg/day), which was reduced gradually as serum thyroid hormone concentrations declined. Re-evaluation was performed with venous blood sampling at least 4 months after restoration of euthyroidism. We evaluated the effect of thyroid hormone replacement therapy on laboratory parameters and plasma visfatin levels in 16 hypothyroid patients who wanted to continue with the study. We also evaluated the effect of antithyroid treatment on laboratory parameters and plasma visfatin levels in 25 hyperthyroid patients who also wanted to continue with the study. Standing height and body weight were measured in light indoor clothing without shoes. Body mass index (BMI) was calculated as weight divided by squared height (kg/m²). The tubes were promptly centrifuged, and the plasma was separated and stored at –80 C. All samples were run in the same assay. Plasma visfatin levels were determined by enzyme linked immunosorbent assay (ELISA) method (Human visfatin C-terminal ELISA kit, Phoenix Pharmaceuticals, Belmont, CA, USA) [sensitivity: (minimum detectable concentration) = 1.85 ng/ml, intra-coefficient of variation: 5% and inter-coefficient of variation: 12%, linear range 1.85-19.5 ng/ml].

Fasting plasma glucose, total cholesterol, triglyceride, and HDL-cholesterol levels were measured by the enzymatic colorimetric method with an Olympus AU 600 auto analyzer using reagents from Olympus Diagnostics, GmbH (Hamburg, Germany). Serum TSH, free T4 (f-T4), and free T3 (f-T3) levels were also established (Immulite, 2000 auto analyzer by BioDPC, Los Angeles, CA, USA). The LDL-cholesterol level was calculated using Friedwald’s formula (18). The basal plasma insulin level was determined by the coated tube method (DPC, Los Angeles, CA, USA). Insulin sensitivity was determined by the homeostasis model assessment (HOMA) index with the formula: HOMA-IR = fasting insulin (mU/ml) x fasting glucose (mg/dl)/405 (19).

Statistical analysis
All analyses were performed using SPSS/PC statistical program (Version 15.0 for Windows; SPSS, Chicago, IL, USA). Results have been reported as mean±SD for parametric variables and median (min-max) for non-parametric variables. One sample Kolmogorov-Smirnov test was used to evaluate the distribution characteristics of variables. The differences between the groups were tested for significance by one-way analysis of variance test and chi-square tests. Tukey’s test and Bonferroni adjusted Mann-Whitney U-test were used for post-hoc analysis as appropriate. Differences were tested with the non-parametric Wilcoxon’s test for paired observations. Spearman correlation and multiple linear regression analyses were used to investigate the main factors influencing visfatin. Differences and correlations were considered significant at p<0.05.

RESULTS
Demographic variables of controls and patients are given in Table 1. There was no significant difference between sex and age (45.23±7.11 in control group, 43.94±14.27 in hypothyroid group, 45.87±13.28 in hyperthyroid group). Weight and BMI were significantly lower in hyperthyroid patients when compared to hypothyroid and control groups (Table 1).

Plasma levels of TSH, total cholesterol, LDL, triglyceride, HOMA-IR, and BMI were significantly higher in the hyperthyroid group when compared to controls. HOMA-IR was also significantly higher in the hyperthyroid group. Markedly low visfatin levels were found in hyperthyroid patients (9.44 (8.07-10.8)) compared with the hypothyroid (49.93 (40.7-59.1)) and control groups [38.6 (30.6-46.6]) (p<0.0001, p<0.0001) (Table 1). No statistically significant differences were found between hypothyroid patients and euthyroid controls. There was no difference between visfatin levels according to sex either. When we divided the