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Serum visfatin levels in acromegaly: Correlation with disease activity and metabolic alterations☆,☆☆,★

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ABSTRACT

Objective: The studies that have extensively evaluated the relation between adipokines and metabolic parameters in acromegaly treatment are quite discordant. We aimed to evaluate and correlate a set of selected adipokines, known to have a metabolic role, with the disease activity, metabolic status and treatment modalities.
Design: Data of 56 consecutive acromegalic patients (31 M and 25 F; aged 54 ± 12 years), admitted to the section of Endocrinology of the University of Palermo during the years 2005–2014, including 16 newly diagnosed untreated (*ND*), 21 during therapy with somatostatin analogues (*SA*), 12 with pegvisomant (*PE*) and 7 after surgical treatment (*SU*), grouped into uncontrolled (*group A*: No. 33) and controlled (*group B*: No. 23) were evaluated. Anthropometric and metabolic parameters, insulin sensitivity indexes, visceral adiposity index (VAI), leptin, soluble leptin receptor, adiponectin, visfatin, resistin, adipsin and non-esterified fatty acids (NEFAs) were assessed. In a subgroup of 21 subjects, the insulin sensitivity index (M value) derived from euglycemic clamp was calculated.
Results: Group A showed higher Homa-IR ($p < 0.001$), VAI ($p < 0.001$), triglycerides ($p < 0.001$), visfatin ($p < 0.001$), and NEFAs ($p < 0.001$) and lower ISI Matsuda ($p < 0.001$), M value ($p < 0.001$), HDL cholesterol ($p < 0.001$) and leptin ($p < 0.001$) than *group B*. *ND* patients showed higher VAI, triglycerides, Homa-IR, and visfatin and lower ISI Matsuda, M-value, and leptin compared to other groups (all $p < 0.050$), while no differences were found among *SA*, *PE* and SU patients. IGF-1 ($p = 0.048$), M-value ($p = 0.0029$) and VAI ($p = 0.010$) were independently associated with visfatin, while only ISI Matsuda ($p = 0.019$) was associated with leptin.
Conclusions: In acromegaly visfatin could be considered a useful index of disease activity and metabolic alterations, such as insulin resistance and adipose dysfunction, regardless of the type of treatment.

1. Introduction

The growth hormone (GH) has metabolic effects on peripheral tissues in addition to the growth promoting role, including the stimulation of gluconeogenesis and lipolysis, which results in increased glucose and free fatty acid (FFA) levels and the adipose tissue is one of the key target organs of GH action [1–3].

In acromegaly, the GH excess leads to an alteration in adipose tissue distribution and function through a lipolytic effect and an increased FFA flux from adipose to peripheral tissues and this condition appears to be directly associated with disease activity and insulin resistance [4,5]. The white visceral adipose tissue produces different mediators, the adipokines, and a strong association between metabolic risk and fat distribution or adipokine levels has recently been documented [6]. The adipose dysfunction, resulting in higher lipolytic activity, changes the production and secretion of adipokines known to play a role in the pathogenesis of low-grade systemic inflammation and insulin resistance [7], leading to a cardiovascular disease and systemic metabolic complications [8,9]. In this view, the relation between GH and adipokine levels could explain the metabolic risk associated with acromegaly, although to date the data on adipokine levels in acromegaly are discordant.

The primary outcome of this study was to evaluate a set of selected adipokines, known to have a metabolic role [10,11], in patients with acromegaly and to correlate them with the disease activity and the metabolic status. In addition, we aimed to investigate the effect of different treatment modalities on adipokine levels.

2. Materials and methods

This is a cross-sectional study. For the purpose of the study we analyzed the data of fifty-six outpatients (31 males and 25 females; aged 54 ± 12 years, range 25–79) with acromegaly, admitted to the

Abbreviations: ND, newly diagnosed; SA, somatostatin analogues; PE, pegvisomant; SU, surgical treatment; VAI, visceral adiposity index; NEFAs, non-esterified fatty acids.

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section of Endocrinology of the University of Palermo during the years 2005–2014.

A subset of patients was already included in our previous study aimed to investigate leptin and adiponectin levels in newly diagnosed acromegalic patients [4]. In the current study we have performed a more detailed analysis, by including other adipokines, in a larger group of patients and during different treatment modalities, to avoid reporting data already published. Therefore, in this paper the case load includes only 16 of 24 patients previously published and the other cases are entirely unpublished. The duration of disease was established by patient interview, patients' clinical pictures and onset of osteoarticular symptoms. Patients with mixed GH/PRL-secreting adenoma and with deficiency of one or more anterior pituitary hormones were excluded from this study to avoid the potential impact of hormonal deficit or replacement therapy on GH, insulin growth factor-1 (IGF-1), as well as metabolic parameters.

Sixteen patients were newly diagnosed (*ND*), while the remaining were treated with somatostatin analogues (*SA*, 21 patients) and pegvisomant (*PE*, 12 patients) or had undergone surgery 6 months previously (*SU*, 7 patients). Specifically, among patients treated with SA, 14 (67%) received octreotide long-acting release (LAR) (10–40 mg every 28 days) and 7 (33%) lanreotide autogel (ATG) (60–120 mg every 28 days). In the octreotide-group, 6 patients were treated with a monthly dose of 20 mg, 5 with 30 mg, 2 with 10 mg and 1 with 40 mg; in the lanreotide-group, 4 patients were treated with a monthly dose of 120 mg, 2 with 90 mg and 1 with 60 mg of ATG. The activity of disease at the time of the study was confirmed by plasma mean GH profile, elevated age- and gender-corrected plasma IGF-1 levels and non-suppressible GH after OGTT [12]. According to these criteria, all patients were grouped into those with uncontrolled (*group A*: 33 patients, including 16 *ND*, 10 *SA*, 5 *PE*, 2 *SU*) and controlled (*group B*: 23 patients, including 11 *SA*, 7 *PE*, 5 *SU*) disease. Each group of patients was matched by gender, BMI and WC, to avoid the interference of these variables on metabolic evaluation.

At the time of hospitalization, all patients signed a consent form for the scientific use of their data after a full explanation of the purpose of the study. This study was approved by the Institutional Review Board of the Faculty of Medicine, University of Palermo and the identity of the participants remained anonymous during database analysis.

3. Study design

Body mass index (BMI) and systolic (SBP) and diastolic (DBP) blood pressure were measured in all patients. WC was measured at the midpoint between the lower rib and the iliac crest. After an overnight fast, lipid profile (total, HDL- and LDL-cholesterol, triglycerides), hemoglobinA1c (HbA1c), mean fasting plasma GH (at least three blood samples at 30-min intervals) and IGF-1 levels were measured. To normalize IGF-1 in individual patients, we calculated the ratio between the IGF-1 level and the upper limit of the normal (ULN) range for age and gender (normal = ≤1) and the data are presented as IGF-1 ULN. GH levels were not evaluated in patients treated with *PE*. OGTT was performed in all patients by measuring plasma blood glucose, insulin levels and GH every 30 min for 2 h after 75 g oral glucose load. Basal insulin resistance was assessed using homeostasis model assessment of the insulin resistance (Homa-IR) index [13]. Stimulated insulin sensitivity was measured using the insulin sensitivity index (ISI), a composite index derived from the OGTT and validated by Matsuda and De Fronzo [14].

In a subgroup of 21 subjects (11 uncontrolled and 10 controlled, including 7 patients *ND*, 6 *SA*, 4 *PE* and 4 *SU*) on a different day (day-2) a euglycemic hyperinsulinemic clamp was used to determine the insulin-sensitivity. One catheter was placed in a vein on the forearm for administration of insulin and glucose and the second catheter was placed in a vein of the contralateral forearm for blood samples. The clamp was performed under standard conditions, i.e. the plasma insulin concentration was acutely raised with an insulin priming (0–3 min: 113.6 mU/m^2, 3–6 min: 80.2 mU/m^2, 7–10 min: 50.4 mU/m^2 of body surface area) for the first 10 min of the test and maintained by a continuous infusion of insulin infusion (40 mU/m^2 for the remaining 110 min). The rate of peripheral glucose utilization (M value) was calculated by dividing the glucose amount infused during the last 40 min by body weight measured in kilograms (milligrams per kilogram per minute). The plasma glucose concentration was held constant at basal levels by a variable glucose infusion and under the steady-state conditions of euglycemia the glucose infusion rate equalled glucose uptake by all the tissues in the body and it was therefore considered a measure of tissue sensitivity to exogenous insulin [15].

To evaluate the adipose function, in all patients we measured the visceral adiposity index (VAI), differentiated according to sex and calculated as described [16], and the serum levels of leptin, soluble leptin receptor (sOB-R), adiponectin, visfatin, resistin, adipsin and non-esterified fatty acids (NEFAs) after an overnight fast.

All patients affected by impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) were treated with diet alone. Patients with overt diabetes mellitus and those receiving hypoglycemic agents were excluded from this study to avoid the effect of glucotoxicity or of drugs on the adipokine levels and insulin-sensitivity indexes.

3.1. Hormone and biochemical assays

All biochemical data were collected after overnight fasting. Glycemia, HbA1c and lipid levels were measured in our centralized accredited laboratory with standard methods. Serum insulin was measured by ELISA (DRG Instruments GmbH, Germany). The sensitivity of the method was 1 IU/ml. The normal insulin range (IU/ml) was 5–19. GH levels were assayed by immunoradiometric assay (Radim, Pomezia, Italy). The sensitivity of the assays was 0.05 μg/l. The intra- and inter-assay coefficients of variation (CV) were 4.5 and 7.9%, respectively. Serum IGF-1 was measured using immunoradiometric assays (Diagnostic System Laboratories Inc., Webster, TX). The normal ranges (for age) were: 118–475 and 118–450 (21–30), 102–400 and 100–390 (31–40), 100–306 and 96–228 (41–50), 95–270 and 90–250 (51–60), 88–250 and 82–200 (61–70), 78–200 and 68–188 μg/l (≥70) for men and women, respectively. The sensitivity of the assay was 0.8 μg/l. The intra- and inter-assay CVs were 3.4, 3.0 and 1.5%, and 8.2, 1.5 and 3.7% for low, medium and high points on the standard curve, respectively.

The BioPlex Pro Human Diabetes 10-plex assay (BioRad, Milan, Italy) was used to quantitate leptin (ng/ml), resistin (ng/ml) and visfatin (pg/ml). The BioPlex Pro Human Diabetes Adipsin and Adiponectin duplex assay (BioRad, Milan, Italy) was used for adipsin (ng/ml) and adiponectin (μg/ml). Human sOB-R (ng/ml) was assayed using an ELISA sandwich enzyme immunoassay (Human leptin receptor ELISA, BioVendor, Heidelberg, Germany). NEFAs (mmol/l) were assayed using an enzymatic colorimetric method (Randox NEFA assay FA115, Randox Laboratories, County Antrim, UK).

3.1.1. Statistical analysis

The Statistical Packages for Social Sciences SPSS version 17 was used for data analysis. Baseline characteristics were presented as mean ± Standard Deviation (SD); rates and proportions were calculated for categorical data. The normality of distribution of the quantitative variables was assessed by means of the Kolmogorov-Smirnov test. The differences between the two groups of patients (with controlled or uncontrolled disease) were evaluated with the Student's t-test. Continuous variables were analyzed with a one-way ANOVA and the differences between the groups of patients with different type of treatment were evaluated by ANOVA for repeated measures with a Bonferroni test for the post hoc analysis. Simple univariate correlations among continuous variables with normal distribution were determined by Pearson's test. To evaluate the independent variables influencing leptin and visfatin in all acromegalic patients a linear regression model was performed. A p value of <0.05 was considered statistically significant.