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The Serum Profile of Adipokines in Naïve Patients With Diabetes Mellitus Type 2 and Obesity

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Background: The aim of this study was to explore the relationship of serum profile of adipokines with cardiovascular risk factors and anthropometric parameters in patients with diabetes mellitus type 2. *Subjects*: A population of 108 obese patients with DM2 was analyzed. A complete biochemical anthropometric and nutritional evaluation was performed. *Results*: In the analysis with leptin as a dependent variable, the IL-6 and glucose levels remained in the model ($F = 6.2$; $P < 0.05$), with an increase of 5.8 (CI 95%:2.7–7.6) ng/ml with each 1 pg/ml of IL-6 and of 5.2 (CI95%:2.5–5.8) ng/ml with each 1 mg/dl of glucose. In a second model with adiponectin as a dependent variable, the BMI remained in the model ($F = 3.77$; $P < 0.05$), with an decrease of −3.77 (CI 95%:0.53–7.1) ng/ml with each 1 point of BMI. In the third multivariate analysis with IL-6 as a dependent variable, the glucose level remained in the model ($F = 10.1$; $P < 0.01$), with an increase of 0.09 (CI95%:0.06–0.12) pg/ml with each 1 mg/dl of glucose. In the fourth multivariate analysis with resistin as a dependent variable, the CRP remained in the model ($F = 2.51$; $P < 0.05$), with an increase of 0.28 (CI 95%:0.08–0.48) pg/ml with each 1 mg/dl of CRP. *Conclusion*: Serum profile of adipokines is associated with different risk factors in diabetic obese patients. J. Clin. Lab. Anal. 25:409–413, 2011. © 2011 Wiley Periodicals, Inc.

Key words: adipokines; cardiovascular risk factors; diabetes mellitus type 2; obesity

INTRODUCTION

Obesity and insulin resistance are associated with cardiovascular risk factors, including altered levels of inflammatory markers and adipokines (1). Epidemiologic evidence of the high prevalence of obesity and diabetes mellitus type 2 has led, in the last years, to a dramatic increase in research on the role of adipose tissue as an active participant in controlling the body's physiologic and pathologic processes (2). Obese patients could be diagnosed of metabolic syndrome, too. Metabolic syndrome is a cluster of atherosclerotic cardiovascular disease risk factors manifested as central obesity, insulin resistance, dyslipidemia, and hypertension (3).

The current view of adipose tissue is that of an active secretory organ, sending out adipokines that modulate insulin sensitivity, energy expenditure, and inflammation. Adipokines are proteins produced mainly by adipose tissue (4). These molecules have been shown to be involved in the pathogenesis of the metabolic syndrome and cardiovascular disease in obese patients. Resistin is a protein identified by screening for the genes that are induced during the differentiation of the adipocytes. Although the role of resistin in linking human obesity with type 2 diabetes mellitus is thus questionable (5). Interleukin 6 is increased in most animal and humans models with obesity and insulin resistance (6). Adiponectin is an adipocyte-derived collagen-like protein indentified through an extensive search of adipose tissue. Hypoadiponectinemia increased risk of coronary artery disease together with the presence of multiple risk factors, indicating that adiponectin is a key factor of the metabolic syndrome (7). Leptin is a protein secreted primarily from adipocytes. Leptin suppresses food intake and increases

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energy expenditure by enhancing thermogenesis and metabolic rate. Reports suggest that leptin contributes to atheroscleoris and cardiovascular disease in obese patients (8). Most studies of serum profile of adipokines have been conducted in obese patients, with few studies have been conducted specifically in patients with diabetes mellitus type 2 (9,10).

Accordingly, the aim of this study was to explore the relationship of serum profile of adipokines (leptin, adiponectin, resistin, and interleukin 6) with cardiovascular risk factors and anthropometric parameters in obese patients with diabetes mellitus type 2.

SUBJECTS AND METHODS

Subjects and Procedures

A sample of 108 naïve obese patients (BMI > 30) with diabetes mellitus type 2 was analyzed in a prospective way. This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures were approved by the [HURH]. Written informed consent was obtained from all patients. The recruitment of subjects was a nonprobabilistic method of sampling among patients send from Primary Care Physicians with obesity from a Northwest area of Spain (Castilla y León).

Weight, blood pressure, basal glucose, C-reactive protein (CRP), insulin, total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides blood, and adipokines (leptin, adiponectin, resistin, and interleukin 6) levels were measured in fasting condition. Exclusion criteria included active infectious disease, history of cardiovascular disease or stroke during the previous 36 months, total cholesterol > 300 mg/dl, triglycerides > 400 mg/dl, blood pressure > 140/90 mmHg, fasting plasma glucose < 126 mg/dl, as well as the use of drugs to treat diabetes mellitus, insulin, glucocorticoids, antineoplasic agents, agiotensin receptor blocker, angiotensine-converting enzyme inhibitors, psychoactive medications.

Biochemical Assays

Plasma glucose levels were determined by using an automated glucose oxidase method (Glucose analyser 2; Beckman Instruments, Fullerton, CA). Insulin was measured by enzymatic colorimetry (Insulin; WAKO Pure-Chemical Industries, Osaka, Japan) and the homeostasis model assessment (HOMA) for insulin sensitivity was calculated using these values (11). Serum total cholesterol and triglyceride concentrations were determined by enzymatic colorimetric assay (Technicon Instruments, Ltd., New York, NY), while HDL-cholesterol was determined enzymatically in the supernatant after precipitation of other lipoproteins with dextran sulfate-magnesium. LDL-cholesterol was calculated using Friedewald formula. CRP was measured by immunoturbimetry (Roche Diagnostcis GmbH, Mannheim, Germany), analytical sensivity 0.5 mg/dl. Hemoglobine A1c levels were measured by using high-pressure liquid chromatography.

Interleukin 6 was measured by ELISA (R&D systems, Inc., MN) with a sensitivity of 0.5 pg/ml. Normal values of IL6 was 1.12–12.5 pg/ml. Resistin was measured by ELISA (Biovendor Laboratory, Inc., Brno, Czech Republic) with a sensitivity of 0.2 ng/ml and a normal range of 4–12 ng/ml. Leptin was measured by ELISA (Diagnostic Systems Laboratories, Inc., TX) with a sensitivity of 0.05 ng/ml and a normal range of 10–100 ng/ml. Adiponectin was measured by ELISA (R&D systems, Inc.) with a sensitivity of 0.246 ng/ml and a normal range of 865–21,424 ng/ml.

Anthropometric Measurements and Dietary Intake

Body weight was measured to an accuracy of 0.05 kg and body mass index computed as body weight/(height^2). Waist (narrowest diameter between xiphoid process and iliac crest) and hip (widest diameter over greater trochanters) circumferences to derive waist-to hip ratio (WHR) were measured, too. Bipolar body electrical bioimpedance was used to determine body composition (12). Blood pressure was measured twice after a 10-min rest with a random zero mercury sphygomanometer, and averaged.

Patients received prospective serial assessment of nutritional intake with 3 days written food records. All enrolled subjects received instruction to record their daily dietary intake for 3 days including a weekend day. Food scales and models to enhance portion size accuracy were used. National composition food tables were used as reference (13).

Statistical Analysis

The results were expressed as mean ± standard deviation. The distribution of variables was analyzed with Kolmogorov–Smirnov test. Quantitative variables with normal distribution were analyzed with a two-tailed Student's-*t* test. Nonparametric variables were analyzed with the Friedman and Wilcoxon tests. Correlation analysis was performed with Pearson and Spearman tests. A multiple regression model (step by step) was used to study the dependent variables (leptin, adiponectin, resistin, and IL 6). A *P*-value of less than 0.05 was considered statistically significant.

RESULTS

Univariate Analysis

One hundred and eight patients gave informed consent and were enrolled in the study. The mean age was 53.1 ± 10.7 years; the mean BMI was 38.5 ± 4.2. The average time since the debut of diabetes mellitus was 6.8 ± 3.2 months. Sex baseline characteristics of patients were presented in Table 1, with higher insulin and insulin levels in men than women and higher total cholesterol and LDL-cholesterol levels in women than men.

Anthropometric measurements showed an average waist circumference (119.7 ± 13.7 cm), WHR (0.95 ± 0.09), and average weight (107.5 ± 16.5 kg). Tetrapolar body electrical bioimpedance showed the next data; fat free mass (57.6 ± 14.2 Kg) and fat mass (44.9 ± 13.2 kg). Table 2 shows differences between men and women, with higher weight, fat mass, fat free mass, WHR, and waist circumference in men than women.

Serial assessment of nutritional intake with 3 days written food records showed a calorie intake of 1,854 ± 710 kcal/day, a carbohydrate intake of 196.7 ± 81.3 g/day, a fat intake of 90.6 ± 33.2 g/day, and a protein intake of 94 ± 23.7 g/day. Dietary intakes were higher in men than women; calories (2,361.2 ± 912.8 vs. 1,736.5 ± 576.1 kcal/day; $P < 0.05$), carbohydrates (218.0 ± 89.6 vs. 171.3 ± 63.4 g/day; $P < 0.05$), proteins (103.3 ± 29 vs. 83.6 ± 27.9 g/day; $P < 0.05$), and lipids (106.7 ± 55 vs. 78.4 ± 22.8 g/day; $P < 0.05$).

Table 3 shows serum profile of adipokines, only leptin levels were higher in women than men. Table 4 shows the correlation analysis among adipocytokines and other parameters in the global group. Table 5 shows the correlation analysis in men and women. Leptin has a significative correlation with BMI, weight, fat mass, CRP, IL6, SBP in women and only with BMI, fat mass and IL-6 in men. Adiponectin has a significative correlation with leptin in women and weight and glucose in men. IL6 has a significative correlation with BMI, weight, glucose, HOMA, SBP in men and only with BMI, SBP and leptin in women. Resistin has a significative correlation with CRP and IL6 in women and only with CRP in men.

Multivariate Analysis

After univariate analysis, we performed a multivariate analysis with each adipokine as a dependent variable. In this analysis adjusted by age and sex with leptin as a dependent variable, the IL-6 and glucose levels remained

TABLE 1. Clinical and Epidemiological Characteristics of Study Population

Parameters	Male $n = 40$	Female $n = 68$	P
Age (years)	48.4 ± 12.2	54.3 ± 16	ns
BMI (kg/m^2)	38.5 ± 6.3	38.4 ± 7.4	< 0.05
SBP (mmHg)	125.9 ± 8.6	122.1 ± 5.1	ns
DBP (mmHg)	86.8 ± 12.4	86.2 ± 9.3	ns
Glucose (mg/dl)	139.1 ± 11.5	143.4 ± 18.9	ns
Total cholesterol (mg/dl)	196.5+41.9	218.8 ± 37.9	< 0.05
LDL-cholesterol (mg/dl)	115.7 ± 45.5	136.8 ± 40.6	< 0.05
HDL-cholesterol (mg/dl)	51.6 ± 21.3	56.9 ± 19.4	ns
Insulin (mUI/L)	29.9 ± 13.0	17.3 ± 9.1	< 0.05
HOMA	6.4 ± 4.8	5.1 ± 2.8	< 0.05
CRP (mg/dl)	6.4 ± 7.1	6.3 ± 5.1	ns
HBa1C (%)	5.8 ± 0.7	5.7 ± 1.1	ns

CRP, c-reactive protein; SBP; systolic blood pressure; DBP, diastolic blood pressure; ns, no significative; HOMA, homeostasis model assessment.

TABLE 2. Anthropometric Characteristics by Sex

Parameters	Male ($n = 40$)	Female ($n = 68$)	P
Weight (kg)	112.5 ± 18.4	94.7 ± 12.8	< 0.05
Fat free mass (kg)	66.9 ± 16.4	44.3 ± 7.6	< 0.05
Fat mass (kg)	35.6 ± 9.1	48.4 ± 11.5	< 0.05
Waist circumference	121.7+14.2	117.1+12.5	< 0.05
Waist to hip ratio	1.03 ± 0.07	0.93 ± 0.07	< 0.05

TABLE 3. Circulating Adipocitokines

Parameters	Male ($n = 40$)	Female ($n = 68$)	P
Interleukin 6 (pg/ml)	2.42 ± 2.5	2.07 ± 1.9	ns
Adiponectin (ng/ml)	18.3 ± 24.1	20.4 ± 16.4	ns
Resistin (ng/ml)	3.4 ± 1.3	3.9 ± 1.7	ns
Leptin (ng/ml)	41.5 ± 31.8	75.8 ± 80.8	< 0.05

TABLE 4. General Correlation Analysis in the Total Group

Parameters	Leptin	Adiponectin	IL6	Resistin
BMI	ns	ns	$r = 0.58$	ns
Weight (kg)	ns	$r = -0.37$	$r = 0.41$	ns
Fat mass (kg)	$r = 0.41$	$r = -0.41$	ns	$r = 0.40$
Glucose (mg/dl)	ns	$r = -0.42$	ns	ns
CRP (mg/dl)	ns	ns	ns	$r = 0.74$
HOMA	ns	ns	$r = 0.45$	ns
SBP (mmHg)	ns	ns	$r = 0.55$	ns
Interleukin 6 (pg/ml)	$r = 0.53$	ns	ns	ns
Adiponectin (ng/ml)	$r = -0.40$	ns	ns	ns
Leptin (ng/ml)	ns	$r = -0.40$	$r = 0.53$	ns

BMI, body mass index; HOMA, homeostasis model assessment; SBP, systolic blood pressure; ns, no significative. P value of r coefficient is below 0.05 (significative).

TABLE 5. General Correlation Analysis in Men and Females

Parameters	Leptin	Adiponectin	IL6	Resistin
Men				
BMI	$r = 0.40$	ns	$r = 0.57$	ns
Weight (kg)	ns	$r = -0.367$	$r = 0.41$	ns
Fat mass (kg)	$r = 0.59$	ns	ns	ns
Interleukin 6 (pg/ml)	$r = 0.53$	ns	ns	ns
Glucose (mg/dl)	ns	$r = -0.41$	$r = 0.40$	ns
HOMA	ns	ns	$r = 0.45$	ns
SBP (mmHg)	ns	ns	$r = 0.55$	ns
CRP (mg/dl)	ns	ns	ns	$r = 0.59$
Females				
BMI	$r = 0.38$	ns	$r = 0.65$	ns
Weight (kg)	$r = 0.43$	ns	ns	ns
Fat mass (kg)	$r = 0.63$	ns	ns	ns
CRP (mg/dl)	$r = 0.3$	ns	ns	$r = 0.6$
SBP (mmHg)	$r = 0.39$	ns	$r = 0.76$	ns
Interleukin 6 (pg/ml)	$r = 0.67$	ns	ns	ns
Leptin (ng/ml)	ns	$r = -0.58$	$r = 0.67$	ns
Interleukin 6 (pg/ml)	ns	ns	ns	$r = -0.58$

BMI, body mass index; HOMA, Homeostasis model assessment; SBP, systolic blood pressure; ns, no significative. P value of r coefficient is below 0.05 (significative).

in the model ($F = 6.2$; $P < 0.05$), with an increase of 5.8 (CI 95%:2.7–7.6) ng/ml with each 1 pg/ml of IL-6 and an increase of 5.2 (CI95%:2.5–5.8) ng/ml with each 1 mg/dl of glucose. In a second model adjusted by age and sex with adiponectin as a dependent variable, the BMI remained in the model ($F = 3.77$; $P < 0.05$), with an decrease of −3.77 (CI95%:0.53–7.1) ng/ml with each 1 point of BMI. In the third multivariate analysis adjusted by age, sex, and fat mass with IL-6 as a dependent variable, the glucose level remained in the model ($F = 10.1$; $P < 0.01$), with an increase of 0.09 (CI95%:0.06-0.12) pg/ml with each 1 mg/dl of glucose. In the fourth multivariate analysis adjusted by age, sex, and fat mass with resistin as a dependent variable, the CRP remained in the model ($F = 2.51$; $P < 0.05$), with an increase of 0.28 (CI95%:0.08–0.48) pg/ml with each 1 mg/dl of CRP (Table 5).

DISCUSSION

The major finding of this study was that serum profile of adipokines is related with different cardiovascular risk factors and anthropometrical variables in obese patients with diabetes type 2. These associations have different implications with each adipokine and each parameter as shown in the further multivariate analysis.

In the literature, the most important variable that determines leptin concentration is body fat mass (14), with a sex interaction (15). Our study shows higher values of leptin levels in women, and a relationship with fat mass in both sexes. However, in multivariate analysis, leptin levels are associated with fasting glucose and IL 6 levels. As detected in our study, this relationship of leptin with inflammatory markers has been described in patients with diabetes mellitus type 2 (16). The inverse association of leptin and adiponectin levels detected in our univariate analysis has been described previously (17) too. Choppen et al. (17) have described an inverse association between leptin and adiponectin. Perhaps this association could be secondary to the inverse relation of these adipokines with fat mass; direct relation of leptin; and inverse relation of adiponectin.

Adiponectin decreases lipid synthesis and glucose production in the liver and causes decreases in glucose and free fatty acid levels in the blood. In offspring of diabetes mellitus type 2 patients (18), adiponectin was associated with low rates of lipid oxidation. Other authors (19) have described a positive significant correlation of adiponectin levels with HDL-cholesterol and a negative with triglycerides concentrations. The inverse correlation detected between body mass index and adiponectin levels has also been described by other authors (10). Perhaps the difference of these previous results with ours is due to different populations studied, for example; mean BMI or naïve diabetes mellitus in our study and healthy subjects in the other.

Resistin is known to stimulate the expression of other proinflammatory cytokines and several studies have found circulating levels to correlate with markers of inflammation (20). In this study, as in some previous studies (20–23), levels of resistin and CRP were correlated. Cell-culture experiments on isolated monocytes demonstrated that resistin regulates proinflammatory cytokine secretion through the nuclear factor-κ β pathway (24), a master controller of the proinflammatory process.

IL-6 has been implicated in the regulation of energy balance and is considered a potent proinflammatory mediator. Adipose tissue has been estimated that it contributes about 30% of circulating IL-6 and is related with cardiovascular risk factors (25). The association of IL-6 and leptin levels detected in our univariant analysis has been described (10). However, this association disappeared in multivariant model adjusted by age, sex, and fat mass, showing these variables as confounding factors in this spurious association. Only glucose levels remained in the multivariate analysis. The relationship between IL-6 levels and glucose metabolism has been described previously (26). The data of this study are consistent with these findings, namely that IL-6 are related with glucose metabolism.

There were some limitations in this study; first, the cross-sectional design of the study precludes comment on causality in the relationships. Second, the sample size was small, limiting its statistical power for detecting associations. Nevertheless, this study represents a

simultaneous investigation of relationships between serum adipokine profile and cardiovascular risk factors in naïve diabetic patients. To the best of the authors' knowledge, this is the first study in which serum profile of adipokines have investigated in naïve diabetic patients without taking drug. Park et al. (27) investigated the relationship between CRP levels and adipokines in diabetic patients but some of these patients were taking sulfonylureas.

In conclusion, the serum profile of adipokines is related with different cardiovascular risk factors and anthropometric variables in obese patients with diabetes mellitus. Further studies are needed to analyze this unclear topic area with clinical and therapeutical implications.

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