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Circulating leptin, resistin, adiponectin, visfatin, adipsin and ghrelin levels and insulin resistance in postmenopausal women with and without the metabolic syndrome

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ABSTRACT

Objective: To measure serum levels of adipsin, leptin, resistin, adiponectin, visfatin, ghrelin and insulin in postmenopausal women screened for the metabolic syndrome (METS).
Methods: Serum of 100 postmenopausal women was analyzed using multiplex technology for the mentioned analytes. In addition, values for the homeostasis model assessment of insulin resistance (HOMA-IR) were calculated. Comparisons were performed in accordance to the presence or not of the METS and each of its components. Criteria of the American Heart Association were used to define the METS.
Results: Age and time since menopause onset were similar in women with the METS ($n = 57$) as compared to those without the syndrome ($n = 43$). METS women displayed significantly higher levels of adipsin, leptin, resistin, insulin and HOMA-IR values and lower adiponectin levels. These differences were mainly observed among women with abdominal obesity, independent of fulfilling METS criteria or not. In this same sense, lower adiponectin levels significantly related to low HDL-C and high triglyceride levels; and higher insulin and HOMA-IR values related to high triglyceride and glucose levels, respectively.
Conclusion: In this sample, postmenopausal women with the METS displayed higher insulin and adipokine levels. These were mainly related to abdominal obesity and metabolic and lipid abnormalities. More research is warranted in this regard.

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1. Introduction

Ovarian exhaustion during the menopausal transition produces endocrine and metabolic changes that relate to body composition and lifestyle habits, stress, and psychosocial adjustments, all which increase weight and the prevalence of the metabolic syndrome (METS). The adipose tissue is a complex and highly active endocrine organ engaging with multiple functions mainly nutrient homeostasis, energy storage, body insulation, thermogenesis, lipid oxidation, adipokine secretion and anti-atherogenesis [1–3]. Visceral and subcutaneous fat produce a large array of adipokines which display actions on the immune system, endothelium and cardiovascular system, metabolism and inflammation [3–6].

Many women report increasing their appetite during the menopausal transition generally linked to metabolic and mood changes (anxiety), and physical inactivity. The hypothalamus integrates neural and humoral inputs that provide coordinated feeding and energy expenditure responses. Ghrelin secretion is a signal of hunger, and its administration induces energy intake in lean and obese individuals contributing to weight gain [7]. In addition, this gut hormone also stimulates growth hormone secretion and inhibits pro-inflammatory cytokine secretion [8].

The METS is a chronic condition related to lifestyle habits that affects a quarter of women and males worldwide [9]. It is a cluster of factors closely related to obesity, increased inflammation, insulin resistance, metabolic and lipid abnormalities, prothrombosis, endothelial dysfunction, oxidative stress, macro- and microvascular abnormalities and atherogenesis all which

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increase cardiovascular disease, cancer and mortality risk [10–13]. The increasing prevalence of excessive body weight, the METS and associated morbidities in mid-aged women represents an important health problem. Since there is limited data regarding postmenopausal METS and adipokine and metabolic abnormalities the present study aimed at measuring the levels of several adipokines, ghrelin and insulin in postmenopausal women without and with the METS and its components.

2. Methods

2.1. Participants and study design

From December 2011 to June 2012 a METS screening program was carried out at the Institute of Biomedicine of the Medical Faculty of the *Universidad Católica de Santiago de Guayaquil*, Guayaquil, Ecuador [14]. Through newspaper advertising a total of 204 natural postmenopausal women aged 40–65 participated. All individuals were non-hormone therapy users. Women taking phytoestrogens or drugs intended to decrease lipid levels or had malignant diseases were excluded. The research protocol of the study was reviewed and approved by the Scientific Research Committee of the Institute of Biomedicine. Eligible women were asked to attend the institute to be informed about the study, its purposes and provide written consent of participation. Those consenting and fulfilling the inclusion criteria were asked to return after an 8 h overnight fast, moment in which socio-demographic data and abdominal perimeter, weight, height and blood pressure measurements were recorded. A 10–15 ml peripheral venous blood sample was also obtained.

This document represents a secondary analysis of the serum of 100 participants of the original cohort. Serum was reassessed and analyzed for adipsin, leptin, resistin, adiponectin, visfatin, ghrelin and insulin. Values for the homeostasis model assessment of insulin resistance (HOMA-IR) were also calculated. Analyte and HOMA-IR values were compared in accordance to the presence or not of the METS and each of its components. Primary serum data is presented elsewhere [6].

2.2. Diagnostic criteria for the metabolic syndrome

Diagnostic criteria recommended by the American Heart Association and the National Heart, Lung, and Blood Institute [15] was used to define the METS. This was the case if three or more of five criteria were encountered: abdominal obesity (waist circumference >88 cm), increased serum triglycerides (TG) (≥150 mg/dL), decreased high density lipoprotein cholesterol (HDL-C) (<50 mg/dL), high fasting glucose (≥100 mg/dL, or the use of hypoglycemic agents) and increased blood pressure (≥130/85 mmHg, or the use of antihypertensive medications) [15]. Method for assessing abdominal perimeter has been previously described [14].

2.3. Measurement of the different analytes

Blood samples withdrawn from each participant were centrifuged at 5 °C for 10 min at 3000 rpm. As previously described [6], the obtained serum was treated accordingly to manufacturer instructions, decanted into 0.5 ml aliquots and then stored at −70 °C.

TG, HDL-C and glucose levels were assayed using the enzymatic colorimetric method with a Hitachi 717 automatic photometric analyzer (Roche Diagnostics GmbH, Mannheim, Germany). Adipsin, leptin, resistin, adiponectin, visfatin, ghrelin and insulin concentrations were measured using the Bio-Plex 200 System® (Bio-Rad Laboratories, Inc, CA, USA; at the Bioclarma srl, Turin, Italy) [16] and as previously described [6].

2.4. The homeostasis model assessment of insulin resistance (HOMA-IR)

HOMA-IR values were calculated by multiplying fasting insulin (mIU/L) and glucose (mg/dL) levels and then dividing this product by the constant 405 [17]. Insulin resistance was defined according to obtained HOMA-IR values. For the present analysis, this was the case at a cut-off value of ≥2.60. In addition, two subsets for insulin resistance were defined: borderline high (2.60–3.80) and high HOMA-IR (>3.80) which have previously been defined among Hispanic adults [18].

2.5. Statistical analysis

Statistical analysis was performed using the GraphPad Prism 5.0 (GraphPad Software, Inc, San Diego, CA, USA) and the Statistical Package for the Social Sciences version 21.0 (IBM SPSS, Armonk, NY, USA). Data are presented as mean ± standard deviations, frequencies and percentages. The Kolmogorov–Smirnov test was used to determine the normality of data distribution. In accordance to this, the Mann–Whitney *U* test was used to analyze group differences (continuous data). The chi-square test was used to compare percentages. Spearman coefficients were calculated to determine correlations between studied analyte levels and HOMA-IR values and the components of the METS expressed as numeric variables. Sample size was calculated under the assumptions of the detection of a 30% difference in the levels of at least one analyte, with 80% power at a two-sided alpha level of 0.05. At least 45 cases per group would be required to fulfill these assumptions using the Mann–Whitney test. A p value of <0.05 was considered as statistically significant.

3. Results

A 57% (n = 57/100) of the analyzed serum samples were defined as having the METS and 43% (n = 43) as not (non-METS). Age and time since menopause onset were similar in both studied groups. Women with the METS presented a higher rate of positive diagnostic criteria and significantly higher levels of adipsin, leptin, resistin, insulin and HOMA-IR values and lower adiponectin levels (Table 1 and Fig. 1). Independent of having or not the syndrome (pooled analysis), when analyte levels were compared as to presenting or not each of the METS components it was observed that all the analytes found significantly higher among METS women were specifically found higher in those with abdominal obesity. Lower adiponectin levels were observed in women with low HDL-C and high TG levels; and higher insulin levels and HOMA-IR values related to high TG and glucose levels, respectively (data not shown on Table). Spearman analysis found significant correlations for the aforementioned positive trends.

4. Discussion

The menopausal transition is associated with weight gain, dyslipidemia, insulin resistance and the susceptibility of developing the METS [19–21]. The present study found that postmenopausal women with the METS displayed significantly higher levels of leptin, resistin, adipsin, insulin and HOMA-IR values in addition to lower adiponectin levels as compared to those without the METS. Visfatin and ghrelin levels were not significantly different between studied groups. Leptin, ghrelin, adiponectin, and resistin are hormones that have a major role in energy regulation, glucose and

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