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Adiponectin, body mass index and hepatic steatosis are independently associated with IGF-I status in obese non-diabetic women

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ABSTRACT

Objective: Low IGF-I levels have been associated with obesity, insulin resistance, hepatic steatosis, and were shown to predict cardiovascular mortality. Adiponectin, on the other hand, was proved to have an important protective role against metabolic and cardiovascular diseases. This study investigates the relation between hepatic steatosis, adiponectin and IGF-I levels in a group of non-diabetic obese Romanian women.

Design: This cross-sectional study included 201 obese non-diabetic women, with mean age of 41.1 ± 11.9 years and mean body mass index (BMI) of 44.1 ± 8.3 kg/m^2, consecutively admitted to the Endocrinology Department of a University Hospital to be evaluated as candidates for bariatric surgery. Main measured parameters included total adiponectin (detected by ELISA method), insulin, C reactive protein (CRP), and IGF-I (all by chemiluminescence methods). Insulin sensitivity was assessed using the Quantitative Insulin Sensitivity Check Index (QUICKI). Patients were considered IGF-deficient if IGF-I z score was ≤2 standard deviations from mean for age. Hepatic ultrasound was used to determine the presence of significant steatosis (SS+).

Results: Significant steatosis was observed in 60.7% of our patients and this feature was associated with reduced total adiponectin levels ($p<0.001$) and lower IGF-I z scores ($p<0.001$). IGF-I z score negatively correlated with BMI ($r=-0.283$, $p<0.001$), alanine aminotransferase (ALT) ($r=-0.130$, $p=0.032$), gamma glutamyltransferase (GGT) ($r=-0.158$, $p=0.018$) and logarithmic transformed (log) CRP ($r=-0.232$, $p=0.001$) and positively correlated with QUICKI ($r=0.148$, $p=0.023$) and log adiponectin ($r=0.216$, $p=0.003$). The relationship between IGF-I z score and log adiponectin remained significant after adjusting for age, BMI, ALT, QUICKI and log CRP ($r=0.183$, $p=0.012$). IGF-I deficiency was present in 33.3% of these obese women. In multivariate logistic analysis, BMI ($p<0.001$), ALT ($p=0.003$), log adiponectin ($p<0.001$) and SS ($p=0.043$) proved to be independently associated with IGF-I deficiency.

Conclusions: Adiponectin is significantly correlated with IGF-I z scores and, along with BMI, ALT and significant steatosis, is independently associated with IGF-I deficiency in obese non-diabetic women.

1. Introduction

Obesity is characterized by important changes in GH/IGF-I axis. Spontaneous and stimulated GH secretion is reduced [1,2], while IGF-I levels are reported by the majority of studies to be low-normal or low [3]. In cross-sectional studies, low serum IGF-I levels have been associated with insulin resistance [4], dyslipidemia and presence of metabolic syndrome [5]. Furthermore, in Rancho Bernardo Study, low IGF-I concentrations have been shown to predict cardiovascular mortality [6].

Hepatic steatosis is commonly observed in obese patients, with a projected incidence of 60–90% among morbidly obese individuals [7], and is considered a further expression of metabolic syndrome [8]. Hepatocytes are the main source of circulating IGF-I, therefore it was assumed that hepatic steatosis plays a major role in mediating IGF-I axis dysfunction and this association was demonstrated in a large epidemiological study [9].

Adiponectin, the most abundant product of adipose tissue, was proved to have an important anti-inflammatory [10] and anti-atherogenic [11] role. Plasma adiponectin levels are higher in women and are negatively correlated with body mass index (BMI) [12], insulin resistance [13], hepatic steatosis [14] and cardiovascular disease [15]. However, there is little and controversial information regarding the association between plasma adiponectin and IGF-I levels in obese patients.

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The aim of our study was to analyze the relation between hepatic steatosis, plasma adiponectin and IGF-I levels in a group of severely obese women and to establish factors independently associated with IGF-I deficiency in these patients.

2. Materials and methods

2.1. Patients

This study was conducted according to the standards of good clinical practice and the Declaration of Helsinki and was approved by the Ethics Committee of Elias University Hospital. All patients gave a signed informed consent.

The screened study population included 297 obese women (BMI > 30 kg/m^2) consecutively admitted in Elias Hospital Department of Endocrinology, Diabetes and Metabolic Diseases between June 2008 and December 2011 to be evaluated as candidates for bariatric surgery. We decided to limit our analysis to females, to minimize the gender influence on adiponectin and IGF-I levels [12,3]. The exclusion criteria were: ingestion of more than 20 g of alcohol per day (assessed by medical history), any concomitant liver disease (infectious or autoimmune hepatitis, hemochromatosis or Wilson disease, all types of cirrhosis) as well as previous diagnosis of pituitary insufficiency. We also excluded patients younger than 18 or older than 65 years, those regularly taking medication known to be associated with fatty liver or to influence insulin resistance, renal failure, cancer, active infections or chronic steroid therapy. Patients with diabetes were excluded due to the impact of this complication on IGF-I levels [16]. According to these criteria, 201 patients were included in the study.

2.2. Study protocol

Patient work-up included medical history and physical examination, biochemical and endocrine tests, and abdominal ultrasound. Body weight was measured in light clothing and without shoes to the nearest 0.5 kg; height was measured to the nearest 0.5 cm; waist circumference (WC) was measured at the midway between the lower border of the rib cage and the iliac crest. After overnight fasting, blood samples were obtained and used for the determination of glucose, alanine aminotransferase (ALT), aspartate aminotransferase (AST), GGT (gamma glutamyltransferase), total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, and triglycerides (TG). In all patients not previously diagnosed with diabetes mellitus we performed a 75 g oral glucose tolerating test (OGTT), with blood samples taken at 0 and 2 h, to exclude the presence of diabetes.

Hepatitis B surface antigen (HBs Ag) and antibodies to hepatitis C virus (HCV) were assessed for every patient. In selected cases (increased liver enzymes level) we performed specific tests to rule out autoimmune hepatitis. All patients found positive for liver diseases other than steatosis were excluded from the study.

Serum samples of insulin, C reactive protein (CRP) and IGF-I were assayed using a two-site, solid-phase, enzyme-labeled chemiluminescent immunometric assay (Immulite 2000, Siemens Healthcare Diagnostics Products Ltd.). For IGF-I, the analytical sensitivity was 20 μg/l, the intra-assay CV was 2.3–3.9% and the inter-assay CV was 3.7–8.1%. Since IGF-I levels are age-dependent, we calculated the standard deviation score of IGF-I levels according to age (z score). Age-adjusted IGF-I values were referenced from a previously published study by Elmlinger et al. [17], using the same assay utilized in this study. Patients were considered IGF-I deficient if IGF-I z score was ≤ −2 SD from the mean for age.

Insulin sensitivity was assessed using the Quantitative Insulin Sensitivity Check Index (QUICKI) determined according to the equation QUICKI = 1 / (log insulin (mIU/ml) + log glucose (mg/dl)) [18].

Serum adiponectin levels were measured using an ELISA kit (DRG Instruments, Germany). The sensitivity was 0.39 mg/l, the intra-assay CV was 0.9–7.4% and the inter-assay CV was 2.4–8.4%.

Patients were considered to have metabolic syndrome according to the ATPIII definition [19] if they have least 3 of the following 5 risk factors: abdominal obesity or waist circumference greater than 88 cm; serum triglyceride level of at least 150 mg/dl or on treatment; HDL-cholesterol level less than 50 mg/dl or on treatment; blood pressure of at least 130/85 mm Hg or on treatment; and serum glucose level of at least 110 mg/dl.

Sonographic measurements were performed by the same observer, using a Siemens SONOLINE G40 ultrasound system, with a 3.5-MHz vector transducer, to investigate the presence of liver steatosis ("bright liver"). Patients were scanned under fasting condition, in the supine and left lateral position, using subcostal and intercostal approaches. Liver steatosis was assessed based on a hyperechogenicity scale: 0 = absent, 1 = mild, 2 = moderate, 3 = severe, reflecting the difference between the echogenicity of the liver and the right renal cortex. Based on this scale, significant steatosis (SS) was considered present for scores above 2 and absent for scores 0 and 1.

2.3. Statistics

The SPSS software (SPSS Inc. Chicago IL), version 17.0, was used to perform all statistical analyses. Because serum CRP and adiponectin levels were non-parametrically distributed, their levels are expressed as medians (interquartile range) and were transformed to their logarithms before simple or multiple regression analysis. Continuous variables with normal distribution are expressed as means ± SD. Between group comparisons were carried out by means of parametric or non-parametric tests, as appropriate (independent samples t test/Mann–Whitney U test for continuous variables, Pearson's chi squared test for categorical ones). Correlations were performed using Pearson analysis and logistic regression was used to identify the influence of different parameters on the presence of IGF-I deficiency. The overall validity of the model was measured using area under the receiver operating characteristic curve (AUROC) with 95% confidence interval (CI). $p<0.05$ was considered statistically significant for all tests.

3. Results

3.1. Patients clinical and biological characteristics, according to the presence of significant steatosis (SS)

A total number of 201 women were included, with a mean age of 41.1 ± 11.9 years and a mean BMI of 44.1 ± 8.3 kg/m^2. Significant steatosis was present (SS+) in 122 patients (60.7%). Compared to those without significant steatosis (SS−), SS+ patients were older ($p=0.013$), had higher BMI ($p<0.001$) and a more unfavorable metabolic profile (as regards the TG—$p=0.014$, glucose—$p=0.032$ and insulin—$p<0.001$ levels, as well as insulin sensitivity, expressed by QUICKI—$p<0.001$; Table 1). Patients with significant steatosis had higher levels of CRP ($p<0.001$) and an increased prevalence of metabolic syndrome (68.8% in SS+ patients vs 45.5% in SS− patients, $p<0.001$). Adiponectin levels ($p<0.001$) and IGF-I z score ($p=0.003$) were lower in SS+ obese women (Table 1).

3.2. Association between IGF-I z score and relevant anthropometric and metabolic parameters

In bivariate analysis, IGF-I z score negatively correlated with BMI ($r=-0.283$, $p<0.001$), WC ($r=-0.196$, $p=0.002$), ALT ($r=-0.130$, $p=0.032$), GGT ($r=-0.158$, $p=0.018$) and log CRP ($r=-.232$, $p=0.001$) and positively correlated with QUICKI ($r=0.148$, $p=0.023$) and log adiponectin ($r=0.216$, $p=0.003$) (Fig. 1). The association between BMI and IGF-I z score remained significant even after adjusting