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The fatty acid binding protein-4 (FABP4) is a strong biomarker of metabolic syndrome and lipodystrophy in HIV-infected patients

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Abstract

Background: The incidence of metabolic abnormalities in HIV-infected patients is increasing. Fatty acid binding protein-4 (FABP4) is an emerging biomarker for metabolic-related disturbances. We aimed to study FABP4 as a marker of metabolic syndrome (MS) or lipodystrophy (LD) in HIV patients.

Methods: FABP4 plasma concentrations were measured by enzyme-linked immunoassays in 183 HIV-infected patients, enrolled as part of a study aimed at identifying predictors of atherosclerosis. The presence of MS or LD was diagnosed according to standard clinical methods. Univariate and multivariate statistical analyses were performed.

Results: FABP4 concentration was significantly higher in those patients with either MS or LD criteria than those without any metabolic disturbance. Similarly, FABP4 concentration significantly increased with an increasing of MS features and was strongly correlated with body-mass index, triglycerides, HDL-cholesterol concentrations, insulin and blood pressure. Patients in the highest quartile of FABP4 presented a six-fold increased odds ratio for MS and a three-fold increased odds for LD, adjusted by age, sex, body-mass index and the antiretroviral therapy.

Conclusions: FABP4 is a strong plasma marker of metabolic disturbances in HIV-infected patients, and therefore, could serve to guide therapeutic intervention in this group of patients.

Keywords: FABP4; HIV infection; Lipodystrophy; Metabolic syndrome; Metabolic biomarkers

1. Introduction

The use of highly active antiretroviral therapy (HAART) in HIV-infected patients has been associated with insulin resistance [1], unfavorable fat distribution [2] and dyslipidemia [3]. This cluster of metabolic disturbances represents a well-known cardiovascular risk situation, the metabolic syndrome (MS) [4]. The prevalence of MS among the HIV-infected population ranges from 17 to 41% [5,6] and several factors have been implicated, including the direct effect of the virus itself on special features of the MS [2]. Additionally, some HIV-infected patients present with lipodystrophy (LD), that essentially relies on metabolic disturbances (hypertriglyceridemia [7], insulin resistance [8] and low levels of HDL-cholesterol [9]). Therefore, LD may worsen both metabolic variables and atherosclerosis development [10] and tools for its early identification are warranted, since, most of them are prone to be modified by therapeutic strategies.

Recently, several molecules derived from adipose tissue and referred to as adipokines have been proposed to be biomarkers of MS. The adipocyte fatty acid binding protein (FABP4) is a new adipokine that functions by carrying fatty

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acids (FA) from the cytoplasm to the nucleus, where the FA act as PPARγ ligands [11]. FABP4 protects against obesity-related insulin resistance in mice [12], and it is also involved in inflammatory responses [13]. Recent studies have linked the plasma concentration of FABP4 with obesity and some components of the metabolic syndrome [14], and with the development of MS in diabetic patients [15].

We, therefore, aimed to study the role of plasma FABP4 as a marker of MS or LD in HIV-infected patients.

2. Patients and methods

The study was performed in a cohort of HIV-infected patients receiving medical assistance in Hospital Universitari Sant Joan, Reus, Spain. These patients were enrolled and blood samples were taken in 2002, with the aim of investigating atherosclerosis and its related factors [16]. We defined the presence of MS based on the ATPIII criteria, i.e., participants with three or more of the following criteria at recruitment were diagnosed of MS: obesity assessed by body-mass index $\geq$30 kg/m^2; triglycerides $\geq$1.6 mmol/L; HDL-cholesterol <1.04 mmol/L in men and <1.29 mmol/L in women; blood pressure $\geq$ or 130/85 mmHg and/or pharmacological treatment and fasting glucose $\geq$5.6 mmol/L and/or pharmacological treatment [17]. Lipodystrophy was defined as the presence of body-fat changes that could be clearly recognized by the patient and confirmed by the doctor. Body-fat changes included subcutaneous lipoatrophy (hollow cheeks, prominent superficial veins in the limbs or flattening of the buttocks) and central obesity (increased abdominal girth, breast enlargement or dorsocervical fat pad) [18]. Outside of laboratory and genetic analyses, the carotid intima-media thickness (CIMT) was performed and some of these data have already been published [16]. Briefly, we used a GE Logiq 700 with an ultrasound probe of 7–10 MHz, and we identified three segments in the carotid arteries: the common carotid artery (1 cm proximal to the bifurcation), the carotid bulb (in the bifurcation), and the internal carotid artery (1 cm distal to the bifurcation). The far wall IMT images were obtained and digitalized for each participant and the image processing software AnaliSYS TM (Soft Imaging System, Münster, Germany) was applied. IMT measurements on each arterial segment were averaged and used in the statistical analyses as combined IMT.

We recorded data regarding HIV infection, such us opportunistic infections, mode of HIV transmission, CD4 cell count and HIV viral load, and a detailed recording of the antiretroviral medication. Similarly, data concerning classical cardiovascular risk factors and laboratory variables were also included. Blood pressure was determined according to standardized methods. Body-mass index was determined by weight (kg)/height (m^2). Fasting plasma glucose, serum insulin and serum total cholesterol, HDL-cholesterol and triglycerides were measured using the automatic autoanalyzer Synchron LXi 725-Synchron Access Clinical Systems (Beckman Coulter, Fullerton, California, USA) using enzymatic assays and chemiluminescent immunoassays adapted to this system. LDL-cholesterol was calculated using the Friedewald formula. HOMA insulin resistance index was calculated with the following formula: (fasting plasma glucose (mmol/L) $\times$ fasting insulin (mIU/L))/22.5.

CD4+ and CD8+ T cells were determined using FAC scan flow cytometry (Becton Dickinson, Madrid, Spain).

FABP4 plasma concentration was measured using the human FABP4 ELISA kit (Biovendor Laboratory Medicine Inc., Brno, Czech Republic). The assay was conducted according to the manufacturer's instructions. The performance characteristics of these assays were <7% variability intra-assay and <6% inter-assay. Results were calculated using the computerized data reduction of absorbance for the standards versus the concentration, using a four-parameter function and expressed as μg/L.

The independent ethics committee of Hospital Sant Joan approved the study protocol.

2.1. Statistical analyses

Results are expressed as mean (S.D.) or in percentages. The Kolmogorov–Smirnov test was applied to check the normality of the variables. ANOVA was used to test the differences in continuous variables and the chi-square test for those categorical items. We defined the diagnoses of metabolic syndrome or lipodystrophy as dependent variables. We performed forward and backward stepwise multivariate analyses, in which the independent variables were: age, sex, body-mass index and time taking HAART therapy. We also included the plasma concentration of FABP4 in the model.

All p-values reported are two-tailed and those <0.05 denote statistical significance. The SPSS 13.0 package was used to perform the statistical analyses.

3. Results

3.1. Clinical characteristics of participants

The main characteristics of patients enrolled are summarized in Table 1. One hundred and eighty-three HIV-infected patients were included in this study. Twelve fulfilled the criteria for MS, 32 for LD and 17 (9.3%) patients fulfilled both criteria (MS and LD), and they were significantly older than the other groups. Groups with any of the metabolic disturbances, showed significant differences in terms of lipid profile, blood pressure and insulin resistance, although these were not translated in a significant increase in the carotid intima-media thickness.

In Table 2, we summarized the different treatments prescribed. Patients with LD or with LD and MS were exposed to nucleoside reverse transcriptase inhibitors (p = 0.03) for