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Research Article

Adiponectin is better predictor of subclinical atherosclerosis than liver function tests in patients with nonalcoholic fatty liver disease

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Abstract

Adiponectin has recently been considered as a possible link between liver dysfunction and atherosclerosis in patients with nonalcoholic fatty liver disease (NAFLD). The present study was designed to evaluate the relation between circulating adiponectin and arterial stiffness parameters, such as pulse wave velocity (PWV) and aortic augmentation index (AI), in patients with hepatic steatosis. The study group consisted of 52 subjects with NAFLD. PWV and AI were performed using SphygmoCor (version 7.1, AtCor Medical, Sydney, Australia). Metabolic parameters, homeostasis model assessment-insulin resistance, and adiponectin levels were determined. Adiponectin was significantly, positively associated with AI ($r = 0.467$; $P < .0001$) and with PWV ($r = 0.348$; $P = .011$). No association between arterial stiffness parameters and liver function tests was observed. In a multiple linear regression analysis, adiponectin remained a significant predictor of PWV even after controlling for age, gender, and MAP. Serum adiponectin levels were significantly associated with indices of subclinical atherosclerosis, such as PWV and AI in patients with NAFLD. This association was independent of age, gender, and blood pressure level and suggests an active role of adiponectin in the pathophysiology of vascular disease in this particular population group. J Am Soc Hypertens 2014;8(6):376–380.

Keywords: Adiponectin; nonalcoholic fatty liver disease; pulse wave velocity; aortic augmentation index.

Introduction

Insulin resistance has been identified as a potential pathogenic mechanism for the initiation and progression of atherosclerosis in patients with nonalcoholic fatty liver disease (NAFLD).[1–4] Recently, circulating adiponectin, an endogenous insulin-sensitizing hormone, which is highly specific to adipose tissue, has been considered as a possible link between liver dysfunction and atherosclerotic vascular disease in patients with NAFLD.[5]

Although, it has been shown that adiponectin level is inversely associated with hepatic steatosis and predicts its grade and severity,[6,7] beneficial effects of adiponectin could paradoxically disappear in people with advanced liver disease. Recently, it was shown that as hepatic fat declines with advanced fibrosis, adiponectin levels progressively rise, independent of its usual metabolic associations such as insulin resistance, leptin, and body mass index.[8] While the relationship between adiponectin levels and different steatosis grades has been investigated, data has revealed the vascular impact of circulating adiponectin in patients with NAFLD is limited. The vascular adverse changes in NAFLD patients may be assessed noninvasively by arterial pulse-wave contour analysis. These techniques can be regarded as a valid marker of early, preclinical atherosclerosis, as well as a predictor of cardiovascular morbidity and mortality.[9–11] Previously, it has been shown than various liver enzymes, such as ALT, AST, ALP, and GGT were significantly associated with pulse wave velocity (PWV) in subjects with NAFLD; however, significant correlation between adiponectin and PWV was not found.[12] Since adiponectin has recently been considered as a

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possible link between liver dysfunction and atherosclerosis in patients with NAFLD, who have exceptionally high risk of cardiovascular disease, it is critical to understand the impact of adoponectin on vascular function in this population.

The present study was designed to investigate a possible association between serum adiponectin levels and atherosclerotic vascular changes, as determined by PWV and aortic augmentation index (AI) in patients with nonalcoholic fatty liver disease.

Methods

Subjects

In this single-center study, 52 patients (25 males and 27 females) diagnosed with NAFLD were recruited from the outpatient clinic at the Wolfson Medical Center to participate in the study. The diagnosis of NAFLD was based on the results of abdominal ultrasonography and exclusion of viral, autoimmune, or drug-induced liver disease, as well as any alcohol intake of more than 20 g/day. Fatty liver disease was diagnosed on the basis on four sonographic criteria: a diffuse hyperechoic echotexture (bright liver), increased echotexture compared with the kidneys, vascular blurring, and deep attenuation.[13]

Screening procedures included physical examination, complete blood chemistry, complete blood count, urinalysis, and electrocardiography. Patients with a history of unstable angina, myocardial infarction, cerebrovascular accident, or major surgery within the 6 months preceding the study were excluded. All concomitant medications were kept to a consistent routine for up to 3 months to prevent possible effects on the study variables. The patients were instructed to consult the study physician if any change in medical treatment was suggested by another physician. The study was approved by the Institutional Review Board, and the patients signed a full informed consent before participation.

Biochemical Parameters

Blood sampling for full chemistry and metabolic parameters, including fasting glucose, fasting insulin, lipid profile, C-reactive protein, liver function tests, and plasma adiponectin was performed. Glucose was measured using the Aeroset chemistry system (Abbott Diagnostics); high-density lipoprotein cholesterol (HDL) and triglycerides were assayed using an Aeroset automated analyzer (Abbott Diagnostics, Berkshire, UK); low-density lipoprotein cholesterol (LDL) was calculated using Friedewald's formula; and insulin was measured using an immunometric assay specific for human insulin (Invitron, Monmouth, UK). Adiponectin was determined by a commercial sandwich enzyme immunoassay technique (R&D Systems, Minneapolis, MN, USA [catalog number DRP300]) with 2.8% intra-assay and 6.5% inter-assay variability. Homeostasis model assessment-insulin resistance (HOMA-IR) was calculated by the following formula: fasting plasma insulin (mU/mL) $\times$ fasting plasma glucose (mg/dL)/405.

Blood Pressure and PWV Measurement

Blood pressure was measured using an automated digital oscillometric device (Omron model HEM 705-CP, Omron Corporation, Tokyo, Japan), and a mean of three readings was taken. The radial pressure waveform was recorded and subsequently transformed by using a validated generalized transfer function incorporated in the SphygmoCor (version 7.1, AtCor Medical, Sydney, Australia) to give an estimate of the corresponding central ascending aortic pulse wave. With the integral software, the central augmented pressure was calculated as the difference between the early and late systolic peaks of the estimated central pressure waveform. Central AI was calculated as the augmented pressure expressed as a percentage of the pulse pressure. PWV was measured by simultaneous recording of the right carotid and the right radial artery pulse waveforms by two pressure transducers using the SphygmoCor Vx PWV System. This technique, which has been validated for its reproducibility and used extensively, is able to estimate the PWV between the two artery sites.[14]

Statistical Analysis

Analysis of data was carried out using SPSS 9.0 statistical analysis software (SPSS Inc, Chicago, IL, USA; 1999). For continuous variables, such as hemodynamic and biochemistry measures, descriptive statistics were calculated and reported as mean $\pm$ standard deviation. Distributions of continuous variables were assessed for normality using the Kolmogorov-Smirnov test (cut-off at $P = .01$). Associations between continuous variables with approximately normal distributions, including anthropometric, hemodynamic, and arterial stiffness parameters, were described using Pearson's correlation coefficients. Associations between continuous variables with distributions significantly deviating from normal were described using Spearman's rho coefficients. PWV and, separately, AI, were modeled using multiple linear regression analysis. All tests are two-sided and considered significant at $P < .05$.

Results

The clinical characteristics of the study groups are presented in Table 1. The study population was comprised of 27 (52%) females, mean age 53.5 $\pm$ 13 years with diagnosed NAFLD.