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Clinica Chimica Acta 377 (2007) 192–197
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Association of adiponectin and amino terminal proBNP in peripheral arterial disease☆

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Received 1 September 2006; received in revised form 22 September 2006; accepted 23 September 2006
Available online 30 September 2006

Abstract

Background: The aim of the present study was to investigate the relationship of adiponectin, a novel adipocytokine, and amino terminal proBNP (NT-proBNP) in patients with peripheral arterial disease (PAD).
Methods: Serum concentrations of adiponectin and NT-proBNP were measured in 487 patients with symptomatic PAD from the Linz Peripheral Arterial Disease (LIPAD) study.
Results: Correlation analysis revealed an association of adiponectin and NT-proBNP (r, +0.47; $p<0.001$). Even after adjustment for age, sex, body mass index, diabetes mellitus, smoking, arterial hypertension, estimated glomerular filtration rate (eGFR), fasting glucose, LDL-cholesterol, HDL-cholesterol, triglycerides, high-sensitivity C-reactive protein, and total homocysteine the relationship of adiponectin and NT-proBNP remained significant (r, +0.35; $p<0.001$). Furthermore, a subgroup analysis of patients with first manifestation of symptomatic PAD ($n=287$) demonstrated that disease severity (classified by Fontaine stages) was positively related to adiponectin (r, +0.13; $p=0.003$) and NT-proBNP (r, +0.28; $p<0.001$).
Conclusion: Adiponectin was positively associated with NT-proBNP in symptomatic atherosclerotic PAD, independent of traditional and non-traditional risk factors. Moreover, adiponectin and NT-proBNP were related to disease severity, indicating a possible role for assessment of future morbidity and mortality in patients with PAD.

Keywords: Adiponectin; Atherosclerosis; Natriuetic peptides; Peripheral vascular disease; Risk factors

1. Introduction

Atherosclerotic peripheral arterial disease (PAD) is an important manifestation of systemic atherosclerosis, and is characterized by arterial stenosis and occlusions in the peripheral arterial bed of the lower limbs [1,2]. Individuals with PAD have an increased risk of subsequent cardiovascular and cerebrovascular ischemic events and are six times more likely to die within 10 years than patients without PAD [2]. Diabetes mellitus and smoking are the strongest risk factors for PAD [3]. Other well-known risk factors are advanced age, male sex, arterial hypertension, and dyslipidemia [4]. Emerging risk factors for PAD include elevated levels of high-sensitivity C-reactive protein (hs-CRP), and total homocysteine (tHcy) [5].

Adiponectin, an adipocytokine with proposed anti-inflammatory and anti-atherosclerotic properties [6–8], may be another novel candidate. We have recently demonstrated that serum levels of adiponectin were significantly lower in patients with symptomatic PAD than in healthy control subjects, independent of traditional and non-traditional risk factors [9]. Our findings are therefore in line with the current view that hypoadiponectinemia may be implicated in the development of atherosclerosis [10]. Conversely, in very recent studies on patients with known or suspected coronary artery disease high adiponectin levels

Abbreviations: ABI, ankle brachial index; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; LIPAD, Linz Peripheral Arterial Disease; NT-proBNP, amino terminal proBNP; PAD, peripheral arterial disease; tHcy, total homocysteine.

☆ None of the authors has any financial, personal or professional relationship or conflict regarding this article to disclose.

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doi:10.1016/j.cca.2006.09.022

have been associated with all-cause and cardiac mortality [11,12]. These controversial findings indicate that there might be a different impact of increased adiponectin serum levels in populations free of manifest atherosclerotic disease vs. high risk populations.

Even in heart failure, high levels of adiponectin were found to be an independent predictor of mortality [13,14]. In this context, adiponectin has been reported to be positively related to amino terminal proBNP (NT-proBNP) [13,14], a well-established diagnostic and prognostic marker in patients with heart failure and coronary artery disease [15].

As patients with PAD suffer markedly increased morbidity and mortality and as there are currently no published data on the relationship of serum adiponectin and NT-proBNP in patients with symptomatic PAD, we evaluated our data from the Linz Peripheral Arterial Disease (LIPAD) study to investigate the correlation of these two biomarkers in this high risk population, and to assess their association with disease severity.

2. Methods

2.1. Study population

To investigate the relationship of adiponectin and NT-proBNP in patients with symptomatic PAD, we used our data from the Linz Peripheral Arterial Disease (LIPAD) study [16], which was designed to evaluate possible phenotypic and genotypic risk factors for atherosclerotic PAD and to determine the predictive value of risk factors on the long-term outcome of patients with PAD. The study protocol was approved by the local ethics committee in accordance with the Declaration of Helsinki, and all study participants gave informed consent. The LIPAD study objectives, recruitment procedures, and characteristics have been described previously [16]. Four hundred eighty seven consecutive patients with symptomatic atherosclerotic PAD admitted to the St. John of God Hospital in Linz, Austria, for inpatient diagnostics and treatment of chronic limb ischemia were enrolled. Study participants underwent evaluation for the presence of risk factors for atherosclerosis and comorbid conditions, as recommended by Rutherford et al. [17].

PAD was defined as chronic atherosclerotic disease of the lower extremities associated with typical symptoms, such as claudication or leg pain on exertion, rest pain, or minor or major tissue loss, and was verified by interview; physical examination; Doppler segmental blood pressure measurement of the lower limbs, including continuous wave spectral analysis and resting ankle-brachial index measurements; and intraarterial aortofemoral angiography. Patients with PAD were included in the present study on the basis of the final clinical diagnosis established by the attending vascular surgeons. All cases with acute ischemia (i.e., peripheral arterial thrombosis of a native artery, popliteal artery aneurysm, or acutely thrombosed peripheral bypass grafts) were excluded. Additional exclusion criteria were PAD attributable to non-atherosclerotic causes (cardioembolic disease, thromboangiitis obliterans, vasculitis, or congenital or metabolic vascular disease) and a history or presence of any malignancy.

Coronary artery disease was defined as remote myocardial infarction by history, occult myocardial infarction by electrocardiography, previous coronary bypass surgery or percutaneous transluminal coronary angioplasty, and stable or unstable angina and acute coronary syndrome (cardiac troponin positive or negative). Cerebrovascular disease was defined as transient or temporary stroke, completed stroke with permanent neurologic deficit, or acute stroke. Arterial hypertension, diabetes mellitus, and smoking were classified according to recommended standards [17].

2.2. Biochemical analyses

Blood was collected by venipuncture after overnight fasting. Creatinine, fasting glucose, glycohemoglobin A1c, total cholesterol, and triglycerides were analyzed with standard assays on a COBAS Integra analyzer (Roche Diagnostics, Mannheim, Germany). For determination of high-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol quantitative electrophoresis with enzymatic staining (Helena BioSciences Europe, Sunderland, UK) was used. tHcy, folate, and vitamin B12 assays were performed on an AxSYM analyzer (Abbott Diagnostics, Abbott Park, ILL, USA). CRP was measured by a high-sensitivity assay (N High Sensitivity CRP) on a BN ProSpec analyzer (Dade Behring, Marburg, Germany) with polystyrene particles coated with monoclonal antibodies to CRP. Estimated glomerular filtration rate (eGFR) was calculated as recently recommended [18]. Serum samples for adiponectin and NT-proBNP determination were immediately frozen and stored at −80 °C until assessment. Adiponectin was quantified automatically using a commercially available sandwich ELISA (BioVendor Laboratory Medicine Inc., Brno, Czech Republic) on a BEP® 2000 instrument (Dade Behring, Marburg, Germany), as recently described [9]. NT-proBNP concentrations were measured with a fully automated two site (sandwich) enzyme immunoassay with electrochemiluminescent technology on an Elecsys® 2010 instrument (Roche Diagnostics, Mannheim, Germany); the technical properties of this assay have been reported previously [19].

2.3. Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Science software release 13.0 (SPSS Inc, Chicago, ILL, USA). Dichotomous data were given as absolute numbers (%), continuous variables were expressed as median (25th–75th percentiles). Comparisons between patient groups were performed with the Chi-square test and the non-parametric Mann–Whitney U test as appropriate. Pearson correlation coefficients (r) were used to describe the relationship between adiponectin and other clinical and biochemical parameters. Partial correlation coefficients were calculated to determine the association of adiponectin and other parameters of interest independently of possible confounders. Because continuous parameters were generally not normally distributed (as tested by the Kolmogorov–Smirnov test with Lilliefors significance correction), they were logarithmically transformed for all correlation analyses. Probabilities were 2-tailed, and p values <0.05 were regarded as statistically significant.

3. Results

A cohort of 487 patients with symptomatic atherosclerotic PAD (i.e., chronic limb ischemia) was enrolled into the LIPAD study. Patients were admitted because of mild to severe claudication or leg pain on exertion ($n=393$; 81%), ischemic rest pain ($n=17$; 3%), and minor or major tissue loss ($n=77$; 16%). Of the 487 patients with PAD, 153 (31%) had concomitant coronary artery disease and 99 (20%) had concomitant cerebrovascular disease. Furthermore, 113 patients with PAD had >=50% carotid stenosis. Another 20 patients with PAD were classified as having stenosis >=50% as well, because they had undergone previous carotid surgery to treat stenosis. Our study sample included 287 patients with first manifestation of symptomatic PAD and 200 patients with remote percutaneous transluminal angioplasty with or without stenting, vascular surgery, or minor or major amputations.

The clinical and biochemical characteristics are summarized in Table 1. The study comprised 340 male and 147 female subjects with a median age of 70 years. Adiponectin concentrations were significantly higher in women than in men [12.8 mg/L (8.7–17.5) vs. 8.8 mg/L (5.9–12.3); $p<0.001$)]. There was no significant difference in adiponectin concentrations in diabetic compared to non-diabetic patients [8.9 mg/L (6.2–14.2) vs. 9.9 mg/L (6.9–14.2); $p=0.176$]. Median adiponectin levels were not significantly different in PAD patients with concomitant coronary artery disease and/or cerebrovascular disease