Nutrition, Metabolism & Cardiovascular Diseases (2013) 23, 330–336

Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.elsevier.com/locate/nmcd

Nutrition, Metabolism & Cardiovascular Diseases

Increased plasma visfatin concentration is a marker of an atherogenic metabolic profile

T.D. Filippatos [a], V. Tsimihodimos [a], C.S. Derdemezis [a], I.F. Gazi [a], V. Saougos [a], D.P. Mikhailidis [b], A.D. Tselepis [c], M.S. Elisaf [a,*]

[a] *Department of Internal Medicine, School of Medicine, University of Ioannina, Ioannina, Greece*
[b] *Department of Clinical Biochemistry (Vascular Disease Prevention Clinics), Royal Free Hospital campus, University College London Medical School, University College London (UCL), London, UK*
[c] *Laboratory of Biochemistry, Department of Chemistry, University of Ioannina, Ioannina, Greece*

Received 1 December 2010; received in revised form 6 July 2011; accepted 7 July 2011
Available online 2 October 2011

KEYWORDS
Visfatin;
Cardiovascular risk;
LDL subclasses;
HDL subclasses;
Lipoprotein-associated phospholipase A_2;
Paraoxonase;
Apolipoprotein C-III;
Pre-beta1 HDL

Abstract *Background and aims:* Visfatin is associated with atherosclerosis-related diseases. We assessed in non-diabetic individuals the association of plasma visfatin levels with cardiovascular disease (CVD) risk and the atherosclerosis-related metabolic variables.
Methods and results: When study population ($n = 179$, age 49 ± 11 years) was divided according to visfatin tertiles, the 10-year CVD Framingham risk scores were significantly increased in the top visfatin tertile. We observed a positive association between visfatin tertiles with waist circumference and blood pressure, as well as with total cholesterol and triglyceride levels, but not with apolipoprotein C-III, fibrinogen or pre-beta1 high density lipoprotein (HDL). The percentage of large HDL subclasses was significantly lower and the percentage of small HDL subclasses over the HDL-C concentration was significantly higher in the top visfatin tertile compared with the other tertiles. The atherogenic small dense low density lipoprotein subclasses (sdLDL-C) were significantly increased in the top visfatin tertile compared with the lower tertiles. High sensitivity C-reactive protein (hsCRP) concentration was significantly increased in the top visfatin tertile compared with the lower tertiles. Although age and sex distribution did not differ between visfatin tertiles, the simultaneous adjustment for these parameters attenuated the significance of the differences observed in sdLDL-C and hsCRP levels. Similarly, after adjustment for hsCRP or waist circumference, only triglycerides and blood pressure levels, as well as the distribution of HDL subclasses, remained significantly different between visfatin tertiles.
Conclusions: Our results support a role for visfatin in the detection of subjects with many metabolic abnormalities, which result in increased CVD risk.

* Corresponding author. Tel.: +30 2651 0 07509; fax: +30 2651 0 07016.
E-mail address: egepi@cc.uoi.gr (M.S. Elisaf).

0939-4753/$ - see front matter © 2011 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.numecd.2011.07.002

Introduction

Cardiovascular disease (CVD), the main cause of death in developed countries, is mainly associated with the atherosclerotic process. Established risk factors for the development of atherosclerosis include type 2 diabetes mellitus (T2DM), hypertension, hyperlipidemia and smoking [1]. Recent research has shown that there are many other variables that contribute or are associated with atherogenesis. These emerging atherosclerotic risk factors or markers include the distribution of low density lipoprotein (LDL) and high density lipoprotein (HDL) subclasses, enzymes [lipoprotein-associated phospholipase A_2 ($LpPLA_2$), paraoxonase 1 (PON1)] and apolipoproteins (apo, e.g. apoC-III) [2–4].

Human visfatin [nicotinamide phosphoribosyl transferase (Nampt) or pre-beta colony enhancing factor (PBEF)] has been implicated in the pathogenesis of T2DM, obesity, dyslipidaemia, and hypertension and generally of atherosclerosis-related diseases [5]. Our group has previously shown that plasma visfatin levels were significantly increased in subjects with metabolic syndrome (MetS) compared with subjects who did not fulfil the criteria for the diagnosis of the syndrome, independently of the presence or not of obesity [6,7]. However, controversial results exist about the expression, circulating levels and the role of visfatin in the atherosclerosis-related diseases [5,8]. The aim of the present study was to assess the association of plasma visfatin levels with CVD risk, as well as with atherosclerosis-related metabolic variables, such as routine biochemical variables, lipoprotein subclasses and enzymes related to atherosclerotic process.

Methods

Subjects

Consecutive subjects ($n = 179$) attending the Outpatient Lipid Clinic of the University Hospital of Ioannina participated in the present study. All participants gave their informed consent and the study protocol was approved by the institutional ethics committee.

Exclusion criteria

No participant had symptomatic ischemic heart disease (CHD) or any other clinically evident vascular disease (assessed by history, physical examination, electrocardiogram and routine biochemical check). Patients with (i) abnormal hepatic function (aminotransferase activity > 3 times the upper limit of normal, and/or history of chronic liver disease, such as cirrhosis or alcoholic liver disease) (ii) impaired renal function (serum creatinine levels >159 μmol/L, 1.8 mg/dL), (iii) T2DM (fasting blood glucose >7.0 mmol/L, 126 mg/dL), or, (iv) raised thyroid-stimulating hormone (TSH) levels (>5.0 μU/L) were excluded. No participants were receiving drugs that may interfere with glucose or lipid metabolism. For the purposes of this study about 900 individuals with suspected metabolic abnormalities were screened; approximately 700 patients with 1 or more exclusion criteria were excluded.

Determination of anthropometric and metabolic variables

General biochemical variables

All laboratory determinations were carried out following an overnight fast (water only allowed). Serum concentrations of fasting glucose, total cholesterol (TC) and triglycerides (TG) were determined enzymatically on an Olympus AU600 analyzer (Olympus Diagnostica, Hamburg, Germany). HDL cholesterol (HDL-C) was determined by a direct assay (Olympus Diagnostica, Hamburg, Germany). LDL cholesterol (LDL-C) was calculated using the Friedewald formula (provided that TG levels were $<$400 mg/dL; 4.5 mmol/L); nonHDL-C was calculated as TC - HDL-C. Serum apoA-I and apoB levels were measured with a Behring Holding GmbH nephelometer (Liederbach, Germany). ApoC-II and apoC-III were determined by an immunoturbidimetric assay provided by Kamiya Biomedical Company (Seattle, U.S.A).

Fasting serum insulin levels were measured by an AxSYM microparticle enzyme immunoassay on an AzSYM analyzer (Abbott Diagnostics, Illinois, USA). The homeostasis model assessment (HOMA) index was calculated as follows: fasting insulin (mU/L) $\times$ fasting glucose (mg/dL)/405.

The methods used for LDL and HDL subclass analysis and for the determination of pre-beta1-HDL, high sensitivity C-reactive protein (hsCRP), fibrinogen, visfatin concentration, as well as of $LpPLA_2$ activity and PON1 activity are given in detail in an online appendix.

The 10-year risk scores for CVD, CHD, myocardial infarction (MI) and stroke were assessed using the Framingham risk score.

Statistical analysis

Continuous variables were tested for normality by the Kolmogorov–Smirnov test and logarithmic transformations were performed if necessary. Data are presented as mean $\pm$ standard deviation (SD) and median (range) for parametric and non-parametric data, respectively. The possible differences in the gender or age distribution between the visfatin tertiles were tested by chi-squared test and one-way analysis of variance (ANOVA) respectively. ANOVA or Kruskal–Wallis test was used for comparisons between tertiles. Analysis of covariance (ANCOVA) was used to assess the contribution of specific variables in the differences between visfatin tertiles observed using ANOVA. Differences were considered significant at $p < 0.05$. Analyses were performed using the SPSS 15.0 statistical package for Windows (SPSS Inc., Chicago, Illinois).

Results

We enrolled 179 individuals aged 49 $\pm$ 11 (range 27–78) years (Table 1). The distribution of age and gender (males/females) was not different between visfatin tertiles (Table 3).

Cardiovascular risk

The 10-year Framingham risk scores for CHD, myocardial infarction (MI) and CVD were significantly elevated in the top visfatin compared with the lower tertile (Table 2).