Clinical Correlates of Circulating Visfatin Levels in a Community-Based Sample

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Visfatin, a novel adipokine with insulin-mimetic characteristics, is highly expressed in visceral fat (1). Associations of circulating visfatin concentrations with diabetes and obesity have not been rigorously established, most likely due to small sample sizes of prior studies. Furthermore, relations of visfatin to other cardiovascular risk factors in the general population have not been examined systematically. Accordingly, we tested the hypothesis that plasma visfatin would be positively related to obesity, diabetes, and visceral adiposity in a community-based sample.

RESEARCH DESIGN AND METHODS

— The design and selection criteria of the Framingham Third Generation Cohort are detailed elsewhere (2). Briefly, 4,095 adults (53% women; mean age 40 years) having at least one parent in the Framingham Offspring Study cohort were recruited in 2001–2005. At their first examination, participants underwent anthropometry, medical history and physical examination, laboratory assessment of cardiovascular risk factors, and, in a subsample, imaging for coronary calcification and adiposity using multidetector computer tomography (MDCT).

The present study was performed in a subsample of 374 participants (9% eligible; 53% women) in whom plasma visfatin was assayed. We randomly selected these participants using a weighted sampling scheme with oversampling of the lowest and highest sex-specific quintiles of BMI (ratio of 1.5:2:1.5 for the lowest, middle three, and upper quintiles, respectively) using the participants undergoing MDCT imaging as the sampling frame. We chose this sampling strategy for cost efficiency and optimizing the use of nonrenewable serological resources (given the novelty of the biomarker), keeping in mind that prior studies reported both direct (3–9) and inverse (10–12) relations of plasma visfatin to adiposity and diabetes.

Visfatin was assayed using a commercially available ELISA kit (Phoenix Pharmaceuticals, Belmont, CA) (interassay coefficient of variation 4.9%) in plasma samples drawn after an overnight fast and stored at −70° C. Subcutaneous and visceral adipose tissue volumes were measured using an eight-slice MDCT scan of the abdomen (Aquarius 3D Workstation; TeraRecon, San Mateo, CA) consisting of 50 5-mm–thick slices covering 150 mm above the upper edge of S1. Briefly, abdominal adipose tissue was identified semiautomatically based on a threshold algorithm using the nonoverlapping computed tomography attenuations of fatty tissue, muscle, and air as differentiators (13). Covariates and the metabolic syndrome (14) were defined as in Table 1.

Visfatin concentrations were logarithmically transformed to normalize the skewed distribution. Age- and sex-adjusted Spearman partial correlation coefficients were calculated to relate visfatin to cardiovascular risk factors. Due to reports of low and high visfatin levels in diabetes and obesity, we compared the adjusted prevalences of cardiovascular risk factors (modeled as binary variables) in the lowest and uppermost quintiles of visfatin with their prevalence in the middle three quintiles (referent) using χ^2 tests. A two-sided P value of <0.05 was considered statistically significant.

RESULTS

— Clinical characteristics of our sample and correlations of plasma visfatin with cardiovascular risk factors are shown in Table 1. Borderline statistically significant correlations were observed between plasma visfatin and age (positive) and triglycerides (inverse correlation). Visfatin levels were not significantly related to any of the other clinical characteristics or to MDCT-determined visceral or subcutaneous fat. Clinical variables explained <2% (model R^2) of the interindividual variation in visfatin concentrations. Modeling risk factors as categorical variables, we observed an association between the prevalence of hypertension and visfatin ($P = 0.042$). The prevalence of hypertension was lower in both the lowest (18%) and highest (15%) visfatin quintiles compared with those in the referent middle three quintiles (27%). Plasma visfatin was not significantly associated with dyslipidemia, obesity (generalized or abdominal), or diabetes (Table 1). With our sample size, we had 80% power to detect an increment to the model R^2 of 0.024 and to observe a partial correlation coefficient of ≥0.16 (at $\alpha = 0.05$).

CONCLUSIONS

— Previous studies evaluating the correlates of plasma and tissue visfatin have yielded inconsistent results. Some investigators have reported higher plasma visfatin in individuals with

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Received for publication 16 November 2006 and accepted in revised form 21 January 2007.

Published ahead of print at http://care.diabetesjournals.org on 29 January 2007. DOI: 10.2337/dc06-2353.

Abbreviations: MDCT, multidetector computer tomography.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Clinical characteristics* and correlations of plasma visfatin with cardiovascular risk factors*

Continuous measures	Means ± SD	Correlations with log plasma: Spearman's rank coefficient†	Correlations with log plasma: *P*†
Age (years)	45 ± 6	0.09	0.07
BMI (kg/m²)	27.7 ± 6.4	−0.06	0.24
Waist circumference (cm)	95 ± 17	−0.03	0.57
Systolic blood pressure (mmHg)	119 ± 15	−0.02	0.76
Diastolic blood pressure (mmHg)	76 ± 10	−0.07	0.18
Total cholesterol (mg/dl)	191 ± 34	0.03	0.62
HDL (mg/dl)	55 ± 19	−0.09	0.10
Triglycerides (mg/dl)	117 ± 74	−0.09	0.07
Fasting glucose (mg/dl)	99 ± 26	−0.06	0.22
Visceral adipose tissue (cm^3)‡	1,556 ± 960	−0.08	0.13
Subcutaneous adipose tissue (cm^3)‡	2,889 ± 1,621	−0.03	0.63
Visfatin (ng/ml)	30 ± 16		

Categorical measures§	Percentages	Associations with highest or lowest quintile (*P*‖)
Sex (% women)	53	0.96
Obesity	33	0.25
Overweight or obesity	59	0.14
Increased waist circumference	45	0.25
Hypertension	23	0.042
Hypercholesterolemia	14	0.42
Low LDL	31	0.29
Hypertriglyceridemia	29	0.99
Metabolic syndrome	26	0.20
Diabetes	6	0.58
Smoking	13	0.45

**n* = 374. †Values are age- and sex-adjusted Spearman's rank partial correlation coefficients and *P* values for correlations between different cardiovascular risk factors and plasma visfatin. ‡*n* = 355. §Obesity was defined as BMI ≥30 kg/m^2, overweight as BMI 25 to <30 kg/m^2, and increased waist circumference as ≥88 cm (women) or ≥102 cm (men). Hypertension was defined as systolic pressure ≥140 or diastolic pressure ≥90 mmHg or use of antihypertensive agents. Hypercholesterolemia was defined as total cholesterol ≥240 mg/dl or use of lipid-lowering medications. Low serum HDL cholesterol was defined as <50 mg/dl (women) or <40 mg/dl (men), and hypertriglyceridemia was defined as serum concentrations ≥150 mg/dl. Metabolic syndrome was defined according to the modified National Cholesterol Education Program (NCEP) Adult Treatment Panel III criteria by the presence of three or more of the following: increased waist circumference (defined above), elevated blood pressure (≥130 mmHg systolic or ≥85 mmHg diastolic or treatment for hypertension), hyperglycemia (fasting blood glucose ≥100 mg/dl or treatment for elevated glucose), hypertriglyceridemia (defined above), or low HDL cholesterol (defined above). Diabetes was defined as fasting blood glucose ≥126 mg/dl or use of insulin or oral hypoglycemic agents. Smoking was ascertained by self-reported cigarette use during the year preceding the examination. ‖*P* values are from χ^2 tests for associations between the cardiovascular risk factors modeled as binary variables and plasma visfatin concentrations modeled as three categories (comparing prevalence in the lowest quintile and the highest quintile with the middle three quintiles that served as a referent).

gestational (3), type 1 (4,5), or type 2 (5–7) diabetes and obesity (8,9). However, other studies have noted opposite findings, e.g., lower plasma visfatin in gestational diabetes (10) and obesity (11,12). Also, studies relating plasma visfatin to insulin sensitivity or glucose tolerance have reported both direct (1) and no (7,8,11,12) associations. A recent investigation noted a positive relation of plasma visfatin to acute insulin response to intravenous glucose load but not to metabolic risk factors or insulin sensitivity (5). Further, these conflicting findings on correlates of plasma visfatin also extend to reports comparing visfatin expression in visceral and subcutaneous adipose tissue; higher (1) and similar (8) levels have been observed in visceral compared with subcutaneous fat.

In the present study, we did not find statistically significant associations between plasma visfatin and diabetes, obesity (generalized or abdominal and subcutaneous or visceral fat), or dyslipidemia. The biological relevance of the inverted U-shaped relation of visfatin and hypertension we observed is unclear, and it might represent a false-positive finding.

Potential explanations of our negative findings include that ours was a community-based cohort study, whereas prior investigations were smaller case-control studies of patients with diabetes or obesity (3–7,9–12) or based on patients referred to a hospital for abdominal surgery (8). Notably, only 6% of participants in our sample had diabetes, which might have limited our power to detect an association. Further, the lack of association of plasma visfatin with cardiovascular risk factors does not negate an important physiological role for this novel adipokine. There were several limitations of our study. First, we had limited statistical power to detect modest associations given that our study is based on a subsample (9%) of the whole cohort and had a low prevalence of diabetes. Second, plasma visfatin concentrations may not adequately reflect tissue activity. Third, we did not relate plasma visfatin to measures of insulin sensitivity/secretion. Fourth, our sample consisted of middle-aged, white individuals, limiting the generalizability of our findings to other ages and ethnicities. Fifth, since our study was cross-sectional, we cannot assess whether visfatin levels are related to longitudinal tracking of metabolic traits.

Overall, our findings, based on investigation of a moderate-sized community-based sample, suggest that circulating visfatin may not be a useful clinical biomarker of metabolic traits.

Acknowledgments— This study was funded by the Swedish Heart-Lung Foundation and the Swedish Society of Medicine (to E.I.), and the National Heart, Lung, and Blood Institute's Framingham Heart Study (Contract No. N01-HC-25195) Grants K23-HL-074077 (to T.J.W.), RO1-HL-076784 (to E.J.B.), and 2K24HL4334 (to R.S.V.).

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