Original Article

Elevated Serum Visfatin Levels in Patients with Acute Myocardial Infarction

Maryam Mazaherioun MSc[1,2], Mohammad Javad Hosseinzadeh-Attar MD PhD•[1,2,3], Leila Janani MSc[4], Ali Vasheghani Farahani MD[5], Neda Rezvan MSc[1], Zohreh Karbaschian MSc[1], Arash Hossein-Nezhad MD PhD[6]

Abstract

Background: Visfatin, a novel adiopocytokine, has been proven to be a proinflammatory mediator involved in the process of atherosclerosis. Visfatin has been shown to play a role in plaque destabilization as it is found abundantly in foam cell macrophages within unstable atherosclerotic plaques. The present study is designed to investigate the potential association between serum vistafin levels and the risk of acute myocardial infarction (AMI).

Methods: There were 72 patients (mean age: 61.57 ± 11.40 years) as cases who presented with first-time AMI that were assessed 8 hours after the incident. The control group consisted of 83 healthy volunteers (mean age: 60.30 ± 8.32 years). Plasma visfatin levels were measured using enzyme immunoassay in both groups. Biochemical parameters were analyzed. Blood pressure, body mass index (BMI), waist circumference, diabetes, and hypertension were recorded.

Results: Serum visfatin levels were significantly higher in patients with AMI (12.77 ± 8.06 ng/ml) compared to controls (6.57 ± 2.96 ng/ml, $P \leq 0.001$). We found that a visfatin level > 7.244 ng/ml (log visfatin > 0.86) had a sensitivity of 70% and a specificity of 75% for predicting AMI.

Conclusion: We have detected high levels of visfatin in patients with AMI. It can be concluded that proinflammatory cytokines such as visfatin may play a role in the development of atherosclerosis as well as destabilization of the atherosclerotic plaque.

Keywords: Atherosclerosis, cytokines, proinflammatory

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Introduction

Obesity is of paramount importance as a risk factor for atherosclerosis of the coronary arteries, and consequently, for increasing the risk of myocardial infarction.[1] Increasing evidence indicates that adipose tissue, besides its role as an energy storing organ, shows endocrine properties in systemic vascular inflammation.[2] Various pro- and anti-inflammatory mediators and cytokines secreted from adipose tissue are collectively called "adipokines". It has been demonstrated that adipokines regulate different stages of atherosclerosis, from endothelial dysfunction (ED) to plaque destabilization and rupture.[3–5]

Visfatin is a novel adipokine with different functions, for which exist a plethora of research on its characteristics and roles.[6] This adipokine was previously known as PBEF and demonstrated to be an intracellular protein with a key enzyme role in nicotinamide adenine dinucleotide (NAD) synthesis.[6] Visfatin is mainly found in visceral adipose tissue and mimics insulin in lowering plasma glucose levels.[6] It is produced by different lineages of immune cells such as neutrophils and macrophages, and induces expression of TNF-α and IL-6 in human monocytes. Therefore, visfatin can be considered as a proinflammatory adipokine.[7–9]

Recent studies have demonstrated high levels of visfatin in patients with inflammation such as type 2 diabetes mellitus, obesity, metabolic syndrome, and cardiovascular disease.[9,10] Besides, it has been shown that this adipocytokine may have a role in plaque destabilization, the promotion of angiogenesis, and glucose homeostasis.[6,11–13] Therefore, it is reasonable to consider that visfatin should have a role in atherosclerosis and cardiovascular disease.

As myocardial infarction is a life-threatening incident, it seems imperative to investigate any potential serum surrogate marker for atherosclerosis. In this regard, visfatin could be a good candidate. Therefore, this study is designed to assess any potential relationship between blood visfatin levels, anthropometric variables, and known risk factors of atherosclerosis and acute myocardial infarction (AMI).

Materials and Methods

Study population

Our case-control study included 72 patients who presented with AMI for the first time and were assessed 8 hours after the incident. Controls consisted of 83 healthy individuals matched by the "frequency matching method" for age, sex, and body mass index (BMI). Cases presented with AMI from June 2009 through July 2009 to the Tehran Heart Center and controls were randomly selected from participants of one of the Endocrinology and Metabolism Research Institute projects conducted in Tehran. Patients

Authors' Affiliations: [1]Tehran University of Medical Sciences, International Campus, (TUMS. IC), Tehran, Iran, [2]Endocrinology and Metabolism Research Center (EMRC), Obesity and Food Group, Tehran University of Medical Sciences, Tehran, Iran, [3]Department of Nutrition and Biochemistry, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran, [4]Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran, [5]Department of Cardiology, Tehran Heart Center, Tehran University of Medical Sciences, Tehran, Iran, [6]Endocrinology and Metabolism Research Center (EMRC), Tehran University of Medical Sciences, Tehran, Iran.

•Corresponding author and reprints: Mohammad Javad Hosseinzadeh-Attar MD PhD, Dept. of Nutrition and Biochemistry, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran. Tel/fax:+00982188951395, E-mail: Hosseinzadeh.MD.PhD@gmail.com

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with inflammatory diseases, infectious diseases, renal or liver problems, diabetic patients and those with any history of myocardial infarction were excluded.

The study was approved by the internal Ethics Committee of the Endocrinology and Metabolism Research Center of Tehran University of Medical Sciences. All participants formally consented to participate in all stages of the study.

Anthropometric measurements and clinical assessments

AMI was diagnosed based on elevation of myocardial necrotic markers in the serum and ST segment elevation on electrocardiogram. Left ventricular ejection fraction (LVEF) was determined by echocardiography, performed approximately 2 – 5 days after hospitalization. BMI was calculated using the international standard equation (weight/height^2) and recorded as kg/m^2.

Waist circumference was defined as the measurement around the narrowest diameter between the lower costal margin and iliac crest. Hip circumference was defined by measuring around the widest diameter over the greater trochanters. These findings were used to calculate the waist-to-hip ratio (WHR). Blood pressure was measured at least 10 minutes before blood sampling in both groups.

Laboratory assessment

Blood samples were collected from both groups following 10 – 12 hours of fasting. Samples were then centrifuged, coded and stored at -80°C until analyzed.

Serum levels of total cholesterol (TCH), triglycerides, high density lipoprotein (HDL), low density lipoprotein (LDL), and fasting blood sugar (FBS) were measured with enzymatic methods using an auto analyzer (Hitachi 902). A commercially available kit was used to measure serum visfatin levels (Human Visfatin ELISA Kit, AdipoGen Pharmaceuticals, Belmont and Seoul Korea). The intra-assay and interassay co-efficients of variance of this kit were less than < 4.3% and < 7.5%, respectively.

Statistical analysis

The results were reported as mean ± standard deviation and all statistical analyses were performed with the use of computer software (SPSS, version 15, SPSS Institute, Chicago, IL, USA). Baseline variables were compared between two groups using the independent student's t- and chi-square tests.

Distributions of continuous variables were analyzed using the Shapiro-Wilks test for normality. As distribution of variables such as visfatin levels, systolic (SBP) and diastolic blood pressure (DBP), HDL and triglyceride levels, and WHR were little-to-mild skewed toward the right, their log-transformed values were used for analysis.

Correlations between serum visfatin levels and independent variables such as anthropometric, biochemical, and clinical variables were analyzed using Pearson's correlation coefficient. Multiple regression analysis with visfatin as a dependent variable was performed using a backward stepwise method to explore independent correlations.

We used multiple logistic regression analysis to explore any possible association between visfatin levels and AMI, adjusted for other potential confounding factors. We divided the distribution of visfatin in pooled data into quartiles and used it in the model. The 25th percentile of visfatin in the pooled data was 5.28, 50th percentile was 6.61, and the 75th percentile was 11.9. SBP, DBP and HDL levels were dichotomized using appropriate cut-off points (140 mmHg for systolic, 90 mmHg for diastolic, and 40 mg/dl for HDL levels) before being used in the model. The final model was estimated using the backward likelihood ratio method. We included levels of visfatin as quartiles in the model to estimate significant linear trends in a potential association between visfatin and AMI. The Receiver Operating Characteristic (ROC) curve was used to describe visfatin concentrations as a potential diagnostic factor and the optimal cut- off point was estimated. *P*-values less than 0.05 were considered statistically significant.

Results

A total of 72 patients with new onset AMI and no histories of any such prior incident as well as 83 healthy individuals (control group) were recruited for the study. There were 115 male and 40 female participants within the age range of 27 – 86 years (mean = 60.90, SD = 9.806).

Clinical characteristics of the study groups are tabulated in Table 1. There were no statistically significant differences regarding age, sex, BMI, weight, waist circumference, WHR, TCH, LDL, and TG levels between the study and control groups. However, mean SBP, DBP, and FBS was higher in the AMI group (all P = 0.000). HDL cholesterol was higher in controls (P = 0.004) compared to patients with ischemic heart disease.

The most intriguing finding of the study was the higher level of plasma visfatin in patients with AMI (12.77 ± 8.06) versus 6.57 ± 2.96 for the controls (P = 0.000), which remained significantly higher after adjustments for DBP, SBP, HDL, and FBS.

There were no differences in mean plasma visfatin levels between males (12.83 ± 8.31) and females (12.57 ± 7.37) in the AMI group, for males (6.41 ± 2.57) versus females (6.95 ± 3.77) in the control group, and for male (9.53 ± 6.86) andfemale (9.2 ± 6.09) pooled data (P > 0.05 for all).

When concentrations were analyzed as quartiles, elevated concentrations of visfatin were significantly associated with a higher risk of AMI (Table 2), an association that had a linear trend.

As tabulated in Table 3, no significant correlation was found between visfatin serum levels and other factors in the study groups. Using multiple regression analysis, we also found no significant association between visfatin levels and other factors.

The ability of log visfatin to detect patients with AMI was explored using a ROC curve. The area under the ROC curve was 0.74 (95% CI: 0.65 – 0.82). A visfatin value > 7.244 ng/ml (log visfatin > 0.86) had a sensitivity of 70% and a specificity of 75% for detecting individuals with AMI (Figure 1).

Discussion

Our study showed that serum visfatin levels were significantly higher in AMI patients compared to controls. This finding was consistent with other studies[14,15] that have shown visfatin could contribute to atherosclerosis and plaque destabilization which in turn, leads to myocardial infarction.

Prior studies have shown that visfatin which is secreted by visceral adipocytes[16] can stimulate up-regulation of inflammatory cytokines (i.e., IL-6, IL-1b, and TNF-α) and chemokines (i.e., macrophage inflammatory proteins-1a, -1b, and -3a).[17] Visfatin has an association with a pro-inflammatory state that can contribute to a number of pathologic changes such as atherosclerosis.[18–20]

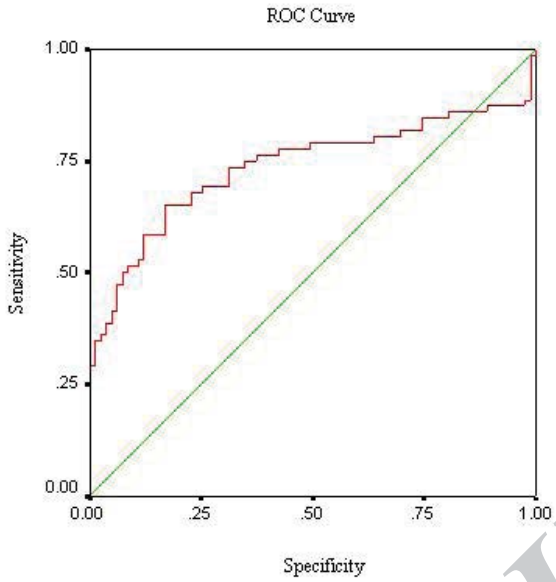

Figure 1. ROC curve used for the definition of the cut-off value of visfatin that best characterizes AMI and control groups.

Table 1. Baseline characteristics of study subjects.

Factor	MI group	Control group	*P*-value
N	72	83	---
Age (years)	61.57±11.40	60.30±8.32	0.44
Sex, male (%)	56 (77%)	59 (71%)	0.34
BMI (kg/m^2)	27.30±4.62	27.32±3.71	0.98
Weight (kg)	76.40±13.44	74.52±9.59	0.31
Waist (cm)	101.18±10.65	102.22±11.01	0.91
SBP[a] (mm Hg)	137.15±23.23	120.35±18.92	0.000
DBP[a] (mm Hg)	86.22±13.06	77.60±10.56	0.000
Cholesterol (mg/dL)	176.40±44.02	178.52±20.28	0.69
FBS (mg/dL)	103.08±13.13	95.28±13.48	0.000
TG (mg/dL)	136.26±70.07	122.72±30.40	0.69
HDL[a] (mg/dL)	40.46±10.81	45.77±12.08	0.004
LDL (mg/dL)	107.77±36.54	112.72±16.58	0.27
WHR[a]	0.99±0.07	1.00±0.123	0.72
Visfatin[a] (ng/mL) concentration[a]	12.77±8.06	6.57±2.96	0.000

Mean±SD was reported; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FBS: Fasting blood sugar; HDL: High density lipoprotein; LDL: Low-density lipoprotein; WHR: Waist-to-hip ratio; [a]Log transformed data were used in t-test.

Table 2. Mulitiple logistic regression analysis with acute myocardial infarction (AMI) as a dependent variable.

Factors	Adjusted OR	(95% CI)	*P*-value
Visfatin			
Quartile 1	---	---	0.000
Quartile 2	0.320	0.099,1.032	
Quartile 3	1.425	0.532,3.815	
Quartile 4	14.856	4.399,50.168	
DBP			
<90	---	---	0.001
≥90	4.73	1.86,11.99	
HDL			
>40	---	---	0.051
≤40	2.35	0.99 , 5.58	
FBS	1.062	1.027, 1.096	0.000

X^2 Hosmer and Lemeshow=4.155 (*P*=0.762); OR for trend (vis)=2.41 (*P*=0.000); DBP: Diastolic blood pressure; FBS: Fasting blood sugar; HDL: High density lipoprotein.

Table 3. Pearson correlation coefficients between plasma visfatin and other variables in study subjects.

Variables	Correlation coefficient	*P*-value
Waist	-0.129	0.280
SBP	0.101	0.211
DBP	0.045	0.571
Cholesterol	-.083	0.303
TG	-.009	0.914
HDL	-.067	0.407
LDL	-.031	0.710
WHR	-.121	0.133
FBS	0.003	0.97

BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FBS: Fasting blood sugar; HDL: High density lipoprotein; LDL: Low-density lipoprotein; WHR: waist-to-hip ratio.

Dahl et al.[11] have shown that "visfatin is strongly expressed within symptomatic atherosclerotic carotid plaques and is localized to areas with lipid-loaded macrophages". Based on this finding, Adya et al. have shown that visfatin, as a potent inducer of MMP2/9, might lead to atherosclerotic plaque instability through activation of NF-kB.[21] Additionally, it is well documented that visfatin is involved in ED, which causes progression of atherosclerosis and therefore plays an important role in different forms of cardiovascular disease.[9]

Our study has shown that a visfatin level > 7.244 ng/ml had a sensitivity of 70% and a specificity of 75% for detecting patients with AMI. We believe that visfatin may be considered as a biomarker for predicting the probability of AMI in the future. Our findings support existing literature regarding the role of visfatin in the process of AMI.

The relationship between visfatin levels and anthropometric and biochemical parameters are not well documented. However, Fukuhara et al.[6] have successfully demonstrated that visfatin levels correlated strongly with visceral fat mass but weakly with subcutaneous fat. Because waist circumference and WHR are good surrogates for visceral fat,[22] we have presumed that there would be a correlation between these values and visfatin levels. Nonetheless, neither previous studies,[16,23] nor ours have found such a correlation. However, a positive correlation between visfatin plasma levels and BMI

has been reported by Berndt et al.[24] Pagano et al.[25] found that obese patients had lower plasma visfatin levels than patients of normal weight, although they failed to explain the reason. Also, our results confirmed the previous finding of no differences between gender,[25] and the lack of an association between visfatin/pre-B-cell colony-enhancing factor (PBEF), SBP and DBP,[26] and lipid profile.[27]

The case-control design limited our ability to infer a causal relationship between increased plasma visfatin levels and AMI.

In conclusion, this report has shown elevated visfatin plasma concentrations in Iranian patients with AMI. A possible close relationship between visfatin, chronic inflammation and the development of atherosclerosis may exist. However, a large-scale prospective cohort study is necessary to determine the potential casual relationship between visfatin and AMI.

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Disclosure statement

The authors have no conflict of interest to declare.

Abbreviations

PBEF1: Pre-B-cell colony-enhancing factor; NAD: Nicotinamide adenine dinucleotide; AMI: Acute myocardial infarction; BMI: Body mass index; LVEF: Left ventricular ejection fraction; TCH: Total cholesterol; TG: Triglycerides; HDL: High density lipoprotein cholesterol; LDL: Low density lipoprotein cholesterol; FBS: Fasting blood sugar; WHR: Waist-to-hip ratio; ROC: Receiver Operating Characteristic.

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