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Association of plasma visfatin with epicardial fat thickness and severity of coronary artery diseases in patients with acute myocardial infarction and stable angina pectoris

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Original Article

Abstract

BACKGROUND: Elevated serum visfatin levels have been reported in some chronic inflammatory diseases such as cardiovascular diseases (CVDs) and rheumatoid arthritis. The purpose of the present study was to investigate the correlation between visfatin and interleukin-6 (IL-6) and anthropometric, angiographic, echocardiographic, and biochemical parameters in patients with acute myocardial infarction (AMI).

METHODS: In this case-control study, 90 patients who were candidates for angiography were divided into the following 3 groups: non-coronary artery disease group (non-CAD; n = 30) with a history of chest pain without angiographic changes, stable angina pectoris group (SAP; n = 30), and AMI group (n = 30). Anthropometric, angiographic, echocardiographic, and biochemical parameters were measured in all subjects.

RESULTS: The mean age of patients in the non-CAD, SAP, and AMI groups was 62.26 ± 13.24, 62.93 ± 8.35, and 52.83 ± 10.26 years (P < 0.001) respectively. The results showed that the median [interquartile range] of visfatin level was higher in the AMI group [7 (6.30-9.30), pg/ml] compared with the SAP [5.85 (5.20-6.60); P < 0.001] and non-CAD [5.20 (3.30-5.70); P < 0.001] groups. In addition, median [interquartile range] IL-6 levels were higher in the AMI group [17.5 (16-21), pg/ml] compared with the SAP [15.50 (14-18); P < 0.01] and non-CAD [14 (11-17); P < 0.001] groups. Furthermore, there was a positive association between plasma level of visfatin, and epicardial fat thickness (EFT) and the Gensini score in the SAP and AMI patients. The results of multivariate linear regression analysis revealed that white blood cell (WBC) count and IL-6 were independently associated with plasma visfatin level.

CONCLUSION: The current study showed an association between visfatin and EFT in AMI patients. Increased visfatin levels in patients with AMI may contribute to atherosclerosis; however, further studies should be conducted to confirm this finding.

Keywords: Visfatin; Adipose Tissue; Echocardiography; Myocardial Infarction; Angina Pectoris; Coronary Angiography

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Introduction

Cardiovascular diseases (CVDs), despite the existence of advanced therapeutics, are still one of the major causes of mortality worldwide.[1] One of the common causes of coronary artery disease (CAD) is atherosclerosis, an inflammatory process that occurs as a result of the accumulation of low-density lipoproteins in the arterial wall.[2] A variety of factors are implicated in the initiation and development of atherosclerosis, such as insulin resistance, metabolic syndrome, obesity, and immune cells.[3-5]

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A large amount of evidence revealed that adipose tissue acts as an endocrine organ by secreting several immunomodulatory proteins known as adipokines.[6,7] In fact, adipokines are potential regulators of the immune system and inflammatory responses in various diseases.[6,8] Adipocytokine levels were shown to increase in some chronic diseases such as rheumatoid arthritis, autoimmune diseases, CVD, asthma, and chronic obstructive pulmonary disease (COPD).[9-11]

Visfatin is an adipocytokine that was first called pre-B-cell colony-enhancing factor (PBEF), and then, named nicotinamide phosphoribosyl transferase (NAMPT) based on its enzymatic function.[12] The main sources of visfatin are monocytes, neutrophils, macrophages, and adipocytes.[13] Various human and animal evidence suggests that visfatin is a pro-inflammatory cytokine that plays a role in regulating immune and inflammatory responses.[14] Elevated visfatin levels were reported in several chronic diseases such as diabetes, asthma, COPD, metabolic syndrome, obesity, CVD, and autoimmunity diseases.[15-18] The findings of previous studies have revealed that the pro-inflammatory effects of visfatin were mainly related to its stimulatory effects on the secretion of inflammatory cytokines such as interleukin-6 (IL-6), IL-1β, and tumor necrosis factor-alpha (TNF-α).[19,20] Interestingly, visfatin is involved in the development of atherosclerosis through leukocyte recruitment and cytokine and chemokine production induction, and plaque instability.[21] The expression of visfatin in epicardial and abdominal adipose tissue of CAD subjects was found to be significantly higher than in that of control subjects, and it was associated with the severity of CAD.[22]

The aim of the present study was to measure serum levels of visfatin and IL-6 in patients with acute myocardial infarction (AMI) and stable angina pectoris (SAP) and compare them with those of the control group (i.e., non-CAD individuals). Moreover, the relationship between serum visfatin levels and epicardial fat thickness (EFT), and other biochemical and echocardiographic parameters was assessed.

Materials and Methods

In the current case-control study, 60 male patients who were previously diagnosed with CAD and were candidates for coronary angiography from March 2018 to June 2019 were enrolled in the study. These patients were divided into two groups namely, AMI and SAP groups (for each group: n = 30). In addition, 30 male patients with a history of chest pain, but normal angiography were recruited as the control group. The sample size was calculated based on the averages comparison formula with $\alpha = 0.05$ and $\beta = 0.1$, $\mu_1 = 6.57$, $S_1 = 8.06$, $\mu_2 = 12.77$, and $S_2 = 2.96$ based on a previous study for serum adipolin levels.[23]

The inclusion criteria for the AMI group were significant elevations in troponin T and creatine kinase-MB (CK-MB), and ST-segment elevation at the J point in at least two adjacent leads. The inclusion criteria for the SAP group were the presence of typical exertion-induced chest discomfort associated with ECG changes during exercise with horizontal ST-segment depression of at least 1 mm. The subjects in the control group had previously experienced chest pain, but had no changes in the electrocardiographic rhythm or significant coronary stenosis as assessed in coronary angiography examination. The exclusion criteria included having a history of hospitalization for ≤ 6 month before the study, having a history of MI, valvular heart diseases, acute or chronic infectious diseases, autoimmune diseases, chronic respiratory diseases, myocarditis, serious heart failure, pericardial effusion, poor echocardiographic imaging, chronic renal failure, hepatitis, cancer, or steroid therapy.

Clinical evaluations: Type 2 diabetes mellitus was defined in the studied patients based on its diagnosis or the need for drug therapy. Subjects with systolic blood pressure (SBP) ≥ 140 mmHg, or diastolic blood pressure (DBP) ≥ 90 mmHg, or those who were being treated with antihypertensive drugs were defined as subjects with hypertension. Hyperlipidemia was defined based on the following criteria: high-density lipoprotein cholesterol (HDL-C) < 35 mg/dl, triglycerides ≥ 150 mg/dl, low-density lipoprotein cholesterol (LDL-C) ≥ 100 mg/dl, or total cholesterol ≥ 200 mg/dl, or those undergoing treatment for lipid disorders.

Demographic characteristics were recorded, and systolic and diastolic blood pressure, height, weight, and abdominal and hip circumference were measured for all participants. Clinical data such as cardiovascular risk factors, medical history, and associated comorbidities were also collected. Body mass index (BMI) and waist-hip ratio (WHR) were also calculated and recorded for all subjects.

Biochemical assessments: In the AMI group, blood samples were collected immediately after admission and used for biochemical assessments. In all groups, blood samples were collected early in the morning after overnight fasting from the subjects in supine

position. Blood samples were collected in tubes containing EDTA. The plasma was immediately centrifuged at 4℃, and then, stored at -80℃ until analysis. Plasma levels of glucose, triglyceride, total cholesterol, HDL-C, LDL-C, blood urea nitrogen (BUN), creatinine (Cr), white blood cell (WBC), hemoglobin (Hb), platelet (Plt), and uric acid were measured using standard commercial methods with a parallel-multichannel analyzer. In addition, serum CK-MB and troponin T levels were measured using the standard methods. Furthermore, the serum concentrations of visfatin and IL-6 were measured using a commercial kit (Crystal day, China) and an electrochemiluminescence method with an automated analyzer (Elecsys 2010, Roche Diagnostics, Basel, Switzerland).

Echocardiography: All echocardiographic assessments were performed by a cardiologist who was blind to the clinical information of the patients. Before performing angiography, echocardiography was performed using a cardiac ultrasound machine (Philips, USA). All echocardiographic test results were recorded and reviewed by two of cardiologists who were blind to the clinical information of the patients. Echocardiographic parameters including left ventricular ejection fraction (LVEF), tricuspid annular plane systolic excursion (TAPSE), tricuspid lateral annular systolic velocity (TV TDI), mitral valve septal annular systolic velocity (e' Septal), and mitral valve lateral annular systolic velocity (e' Lateral) were determined according to the recommendations of the American Society of Echocardiography.

EFT is an echo-free space between the outer surface of the right ventricular (RV) free wall and visceral pericardium. EFT was measured in at least three consecutive beats parallel to the aortic valve and perpendicular to the RV free wall on the side with the greatest thickness on 2D images.[24,25] Images were stored in the echo-machine then evaluated by an echocardiography fellow and two other cardiologists who were blind to the clinical status and angiographic results of the selected patients.

Coronary angiography: Selective left and right coronary angiography were performed via the radial or femoral artery using the standard Judkins technique using 5 or 6 Fr catheters (Medtronic, CA, USA) and an Axiom Artis dFA system (Siemens Corp., Berlin, Germany). The modified Gensini score was used to determine the severity of CAD, which is based on the location and degree of stenosis and used for patients with CAD.[26]

This study was approved by the Ethics Committee of Ardabil University of Medical Sciences, Iran, (IR.ARUMS.REC.1396.206) and conducted from March 2018 to June 2019 at Imam Khomeini Educational and Clinical Hospital, Ardabil, Iran. Before enrollment, written consent was signed by the patients willing to participate.

Statistical Analysis: Normal distribution of data was evaluated using Kolmogorov-Smirnov (K-S) test. The results are presented as mean ± standard deviation (SD), or median and the 25th-75th percentiles. Continuous variables were compared using the Student's t-test. Comparisons between groups were made using the Kruskal-Wallis test. If the difference was statistically significant, it was followed by the Mann-Whitney U test for post hoc analysis; alternatively, ANOVA was performed with the Tukey-Kramer post hoc test. The general linear model (GLM) function analysis was used to adjust for IL-6 level, WBC count, BMI, and WHR. Correlation coefficients were assessed using the Spearman rank order correlation test. Linear regression analyses were performed with visfatin as the dependent variable, and biochemical and clinical findings as the independent variables. A value of $P < 0.05$ was considered to be statistically significant. SPSS software (version 16.0; SPSS Inc., Chicago, IL, USA) and GraphPad Prism software (version 7; GraphPad Software Inc., CL, USA) were used for the statistical analysis.

Results

Demographic, clinical, and biochemical data are presented in table 1. The levels of CK-MB, WHR, troponin-T, LDL-C, and cholesterol were higher in the SAP and AMI groups compared to the non-CAD group. In addition, in the SAP group, SBP was significantly higher compared to the AMI and non-CAD groups, but DBP was only higher than the AMI group. Furthermore, the Gensini score and CK-MB and troponin-T levels were significantly higher in the AMI group compared to the SAP group. The WBC counts were higher in the AMI group compared to the non-CAD group. The AMI patients, SAP patients, and non-CAD subjects did not differ significantly with respect to BMI, heart rate, heart disease history, and smoking, diabetes mellitus, hypertension, and hyperlipidemia status, as well as triglyceride, HDL-C, fasting blood sugar (FBG), BUN, Cr, uric acid, and platelet levels (Table 1).

Plasma Levels of IL-6 and Visfatin: The plasma levels of visfatin were significantly higher in the AMI group compared to the non-CAD and SAP groups ($P < 0.001$ for both; Figure 1a).

Table 1. The baseline characteristics and laboratory findings in the study groups

Variable	Non-CAD (n=30)	SAP (n=30)	AMI (n=30)	P
Age (year)	62.26±13.24	62.93±8.35	52.83±10.26^{**++}	0.001
BMI (kg/m^2)	26.22±2.90	26.88±4.81	27.52±3.67	0.435
Waist circumference (cm)	93.33±5.46	95.40±9.12	97.63±6.33	0.072
Hip circumference (cm)	100.86±7.39	100±8.70	101.53±8.08	0.720
Waist-hip ratio	0.92±0.03	0.95±0.02*	0.95±0.05**	0.003
Systolic BP (mmHg)	120 (115-130)	130 (120-145)*	117 (110-130)$^{++}$	0.001
Diastolic BP (mmHg)	77.5 (70-80)	80 (75-90)*	70 (60-80)$^{++}$	0.002
Heart rate (bpm)	76 (70-85)	74 (70-80)	78.5 (75-80)	0.285
SpO_2 (%)	95 (95-96)	95 (94-96)**	96 (95-96)$^{++}$	0.006
Smoking, n (%)	19 (33.9%)	21 (37.5%)	16 (28.6%)	0.427
Hypertension, n (%)	14 (42.4%)	12 (36.4%)	7 (21.2%)	0.062
Diabetes, n (%)	4 (26.7%)	6 (40%)	5 (33.3%)	0.730
Hyperlipedemia, n (%)	14 (35%)	18 (45%)	8 (20%)	0.121
Familial heart disease, n (%)	15 (36.6%)	15 (36.6%)	11 (26.8%)	0.302
TC (mg/dL)	130.06±33	152.67±39.49*	171.17±36.17***	0.000
TG (mg/dL)	104.77±45.28	128.63±64.95	115.77±51.49	0.243
HDL-C (mg/dL)	38.16±11.93	37.83±9.33	39.53±7.21	0.772
LDL-C (mg/dL)	75.46±19.65	92.63±25.28*	102.17±26.54***	< 0.001
FBG (mg/dL)	98.36±7.68	98.76±6.83	97.43±8.34	0.787
BUN (mg/dL)	36.03±9.07	41.16±13.49	36.23±11.58	0.155
Cr (mg/dL)	1.17±0.23	1.26±0.34	1.26±0.42	0.469
Uric acid (mg/dL)	5.16±1.21	5.95±1.98	6.01±1.80	0.104
Hemoglobin (g/dL)	14.53±1.92	13.94±1.42	14.36±2.11	0.446
WBC (10^3/mm^3)	7.15±1.83	8.19±1.73	8.92±2.48	0.005
Platelet (10^3/mm^3)	2.00±0.50	2.24±0.49	2.14±0.70	0.289
CK-MB (ng/mL)	2.8 (2.5-3.1)	3.55 (3-4)***	33.5 (22-45)$^{***+++}$	< 0.001
HsTnT (ng/L)	2 (1-5)	12.5 (10-14)***	35 (25-46)$^{***+++}$	< 0.001
Gensini score	-	31.40±15.73	44.03±15.51	< 0.001
Visfatin (ng/mL)	5.20 (3.30-5.70)	5.85 (5.20-6.60)**	7 (6.30-9.30)$^{***+++}$	< 0.001
Visfatin (adjusted), (ng/mL)[b]	4.58±0.27	6.17±0.16***	7.58±0.28^{***+++}	< 0.001
IL-6	14 (11-17)	15.50 (14-18)*	17.5 (16-21)$^{**+++}$	< 0.001

Data are expressed as mean ± SD or median (interquartile range). ANOVA was used for parametric data (such as age, BMI, WHR, and biochemical data) and Kruskal-Wallis for non-parametric data (such as systolic and diastolic BP, SpO_2, heart rate, visfatin, and IL-6).

[b]Mean ± SD by general linear model with adjustment for age, BMI, WHR, and smoking status

SAP: Stable angina pectoris; AMI: Acute myocardial infarction; Non-CAD: Non-coronary artery diseases; BMI: Body mass index; BP: Blood pressure; SpO_2: O_2 saturation; TC: Total cholesterol; TG: Triglyceride; LDL: Low density lipoprotein; HDL: High density lipoprotein; FBG: Fasting blood glucose; BUN: Blood urea nitrogen; Cr: creatinine; WBC: White blood cell; AST: Aspartate transaminase; ALT: Alanine aminotransferase; CK-MB: Creatine kinase-MB; HsTnT: High-sensitivity troponin T

For statistical differences between the non-CAD group and other groups: $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$

For statistical differences between SAP and AMI: $^{+}P < 0.05$, $^{++}P < 0.01$, $^{+++}P < 0.001$

The plasma levels of visfatin were also higher in the SAP group compared to the control group (P < 0.001). Interestingly, the plasma visfatin levels remained significantly different among the studied groups (P < 0.001) after adjustment for age, smoking history, BMI, IL-6 level, and WHR (Figure 1b). Moreover, plasma levels of IL-6 were higher in the SAP (P < 0.01) and AMI (P < 0.001) groups compared to the non-CAD group. In addition, plasma IL-6 level in the AMI group was significantly higher than the SAP group (P < 0.01, Figure 1c).

Echocardiography results: LVEF values in the SAP and AMI groups were lower than the non-CAD group (P < 0.001 for both). However, no statistically significant difference was observed between the SAP and AMI groups in terms of LVEF values. Interestingly, EFT values were higher in the SAP and AMI groups than the non-CAD group (P < 0.001 for both). In addition, echocardiographic analysis revealed that EFT was higher in the AMI group compared to the SAP group (P < 0.001; Figure 2a). Furthermore, the EFT value remained significantly different among the studied groups after adjustment for age, BMI, smoking history, and WHR (P <0.001; Figure 2b). Furthermore, the EFT-index results (based on the body surface) showed higher values in the AMI and

SAP groups compared to the non-CAD group (P < 0.001 for both; Figure 2c).

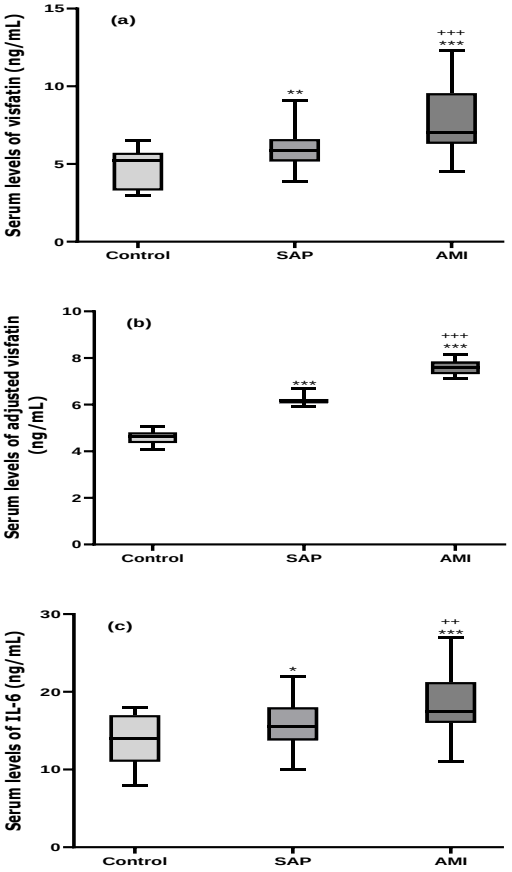

Figure 1. (a): Median (interquartile range) of serum levels of visfatin, (b): adjusted visfatin, and (c): IL-6
The adjustment was performed for age, BMI, WHR, and smoking history in the study groups. For statistical differences between the control group and other groups: $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$
For statistical differences between SAP and AMI: $^{++}P < 0.01$, $^{+++}P < 0.001$

Other echocardiographic parameters such as e' Septal, e' Lateral, and TAPSE showed no significant differences among the groups (Table 2).

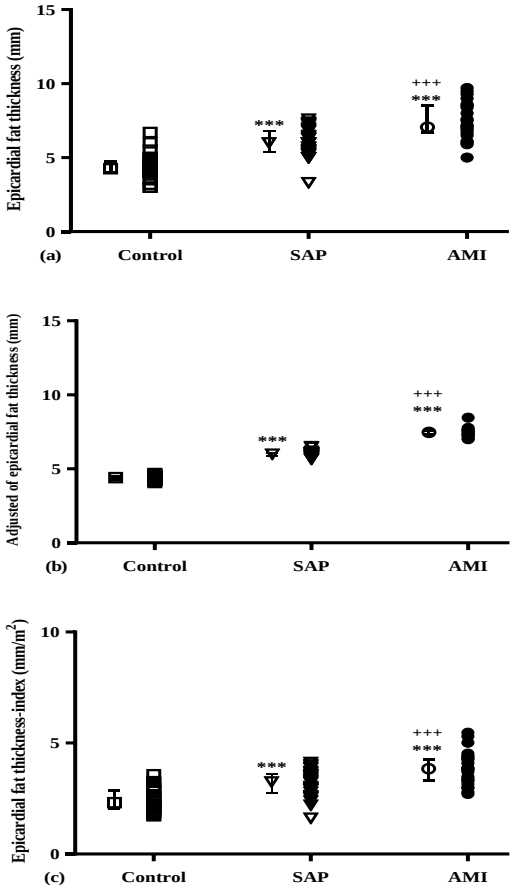

Figure 2. Individual values and mean ± SD of (a): baseline epicardial fat thickness, (b): adjusted epicardial fat thickness, and (c): epicardial fat thickness index
Adjustment was performed for age, BMI, WHR, and smoking history in the study groups. ANOVA (and Tukey's post hoc test) was used to compare groups.
For statistical differences between the control group and other groups: $^{***}P < 0.001$
For statistical differences between SAP and AMI: $^{+++}P < 0.001$

Table 2. Summary of echocardiography in the study groups

Variable	Non-CAD	SAP	AMI	P
LVEF (%)	55 (45-60)	45 (40-50)***	38.5 (30-45)***	< 0.001
e' Septal (cm/s)	6.45 (6-7.5)	5.7 (4.34-7)	6.25 (5.2-8)	0.154
e' Lateral (cm/s)	9.7 (7.9-10.3)	9.1 (7.9-11.6)	8.5 (7.1-10)	0.538
TAPSE (mm)	19.04±3.03	18.01±3.28	17.68±3.16	0.204
TV TDI (cm/s)	11.66±1.50	12.07±1.78	10.92±2.13	0.054
EFT (mm)	4.37±0.78	6.01±0.93***	7.42±1.17^{***+++}	< 0.001
EFT (adjusted), (mm)[a]	4.40±0.14	5.97±0.19***	7.46±0.25^{***+++}	< 0.001
EFT index (mm/m^{2})	2.41±0.48	3.16±0.59***	3.82±0.68^{***+++}	< 0.001

Data are expressed as mean ± SD or median (interquartile range). ANOVA was used for parametric data [such as TAPSE, TV TDI, EFT, EFT index, and EFT (adjusted)] and Kruskal-Wallis for non-parametric data (such as LVEF, e' Septal, and e' Lateral).
[a] Mean ± SD by general linear model with adjustment for age, BMI, WHR, and smoking status
For statistical differences between the non-CAD group and other groups: $^{***}P < 0.001$
For statistical differences between SAP and AMI: $^{+++}P < 0.001$

Association of visfatin with the studied factors: Spearman's rank correlation coefficient revealed that the level of visfatin had a significant relationship with CK-MB ($r = 0.605$; $P < 0.001$; Figure 3a), troponin-T ($r = 0.622$; $P < 0.001$; Figure 3b), Gensini score ($r = 0.419$; $P < 0.001$; Figure 3c), WBC count ($r = 0.381$; $P < 0.001$; Figure 3d), LVEF ($r = –0.461$; $P < 0.001$; Figure 3e), e' lateral ($r = –0.292$; $P < 0.01$; Figure 3f), EFT ($r = 0.510$; $P < 0.001$; Figure 3g), and IL-6 ($r = 0.405$; $P < 0.001$; Figure 3h). However, no significant correlation was observed between the levels of serum visfatin and age, BMI, WHR, SBP, DBP, and heart rate, and oxygen saturation (SpO_2), plasma glucose and lipid, hemoglobin, and platelet levels (Table 3).

In multiple regression analysis, a significant regression equation was found ($F (8,81) = 12.95$; $P < 0.001$) with R^2 of 0.561. Both CK-MB and WBC were significant predictors for visfatin. Indeed, WBC count (β: 0.262; 95% CIs: 0.0001-0.00015; $P < 0.01$) and CK-MB level (β: 0.308; 95% CIs: 0.273, 2.279; $P < 0.05$) were associated with visfatin (Table 4).

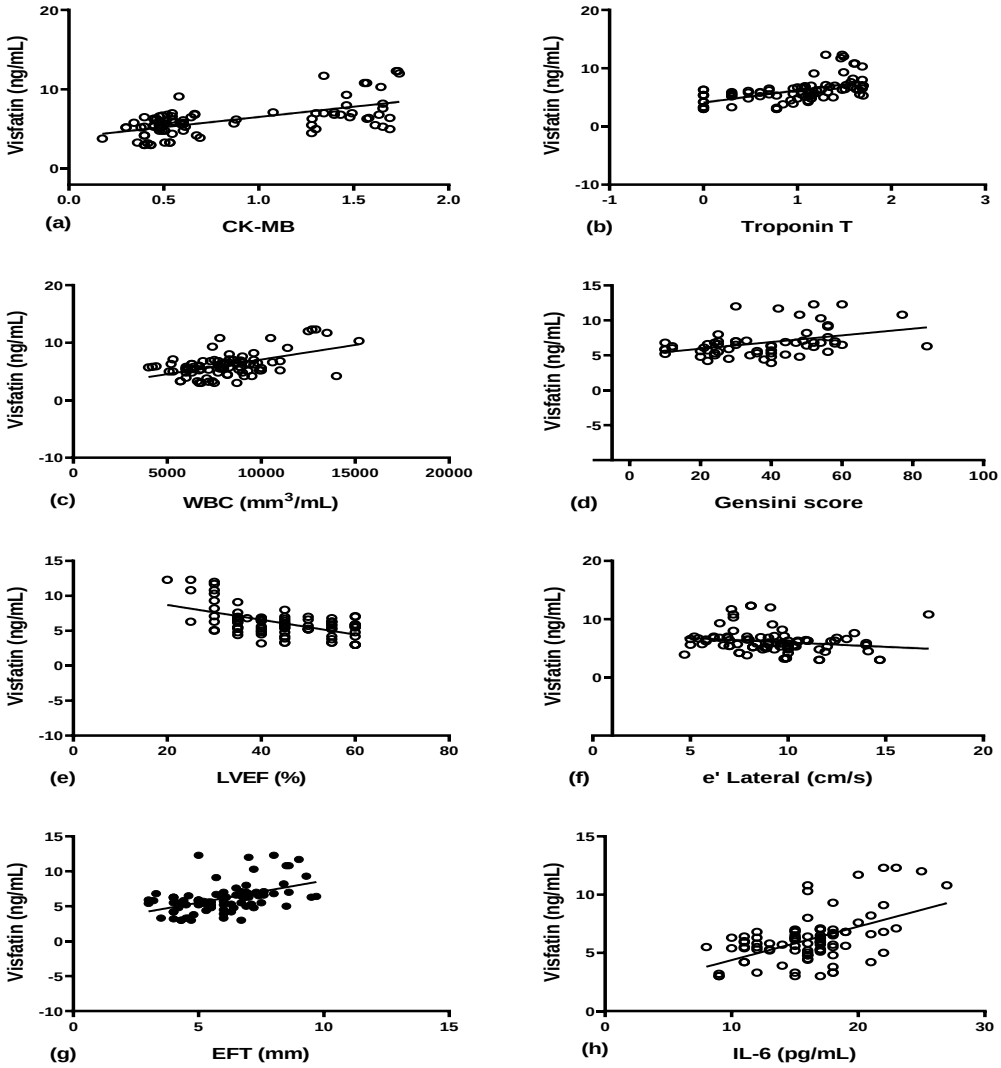

Figure 3. Spearman rank order of (a) visfatin and CK-MB (correlation coefficient = 0.605; $P < 0.001$), (b) visfatin and Troponin-T (correlation coefficient = 0.622; $P < 0.001$), (c) visfatin and WBC counts (correlation coefficient = 0.381; $P < 0.001$), (d) visfatin and the Gensini score (correlation coefficient = 0.568; $P < 0.001$), (e) visfatin and LVEF (%) (correlation coefficient = -0.418; $P < 0.001$), (f) visfatin and e'lateral (correlation coefficient = -0.292; $P < 0.01$), (g) visfatin and EFT (correlation coefficient = 0.510; $P < 0.001$), and (h) visfatin and IL-6 (correlation coefficient = 0.405; $P < 0.001$)

Table 3. Spearman correlation coefficients between basal serum visfatin and relevant parameters in the studied subjects

Variable	Basal visfatin	
	r	P
Age	-0.033	0.758
BMI	0.069	0.518
WHR	0.182	0.085
Systolic blood pressure	-0.150	0.159
Diastolic blood pressure	-0.143	0.177
HR	0.080	0.454
SpO_2	0.205	0.053
FBS	0.043	0.685
T-cholesterol	0.147	0.167
Triglyceride	-0.192	0.069
HDL	-0.132	0.215
LDL	0.184	0.082
CK-MB (ng/mL)[a]	0.605	< 0.001
Troponin T (ng/mL)[a]	0.622	< 0.001
WBC ($10^3/mm^3$)	0.381	< 0.001
Hemoglobin (g/dL)	-0.116	0.227
Platelet ($10^3/mm^3$)	0.021	< 0.001
Gensini score	0.419	< 0.001
LVEF (%)[a]	-0.461	< 0.001
e' Septal (cm/s)	-0.099	0.355
e' Lateral (cm/s)	-0.292	0.005
TAPSE (mm)	-0.081	0.449
TV TDI (cm/s)	-0.023	0.832
EFT (mm)	0.510	0.001
IL-6 (pg/mL)	0.405	< 0.001

BMI: Body mass index; WHR: Waist-hip ratio; SpO_2: O_2 saturation; FBG: Fasting blood glucose; LDL-C: Low density lipoprotein-cholesterol; HDL-C: High density lipoprotein-cholesterol; CK-MB: Creatine kinase-MB; WBC: White blood cell; LVEF: Left ventricular ejection fraction; septal e': Mitral valve septal annular systolic velocity; TAPSE: Tricuspid annular plane systolic excursion; TV TDI: Tricuspid lateral annular systolic velocity; Lateral e': Mitral valve lateral annular systolic velocity; EFT: Epicardial fat thickness

[a] Logarithmic transformation was performed.

Discussion

The main findings of the current study indicated that serum visfatin levels were significantly increased in patients with AMI and SAP, especially in the AMI patients. In addition, there was a positive association between serum level of visfatin and WBC count, CK-MB, troponin-T and IL-6 levels, EFT, and the Gensini score, but a negative association between serum visfatin level and LVEF and e' lateral. Furthermore, the results of multiple regression analysis revealed that WBC count and CK-MB values were independently associated with serum visfatin levels. Moreover, the results indicated that there was a relationship between serum visfatin levels and the severity of CAD based on the Gensini score and EFT in patients with AMI and SAP, especially in the AMI patients.

Table 4. Multiple regression analysis for plasma visfatin with other risk factors

Variable	Multiple regression		
	B	95% CI	P
CK-MB	0.308	0.273-2.279	0.013
Troponin T	0.009	-1.008-1.075	0.949
Gensini score	0.119	-0.015-0.037	0.397
e' Lateral	-0.059	-0.173-0.078	0.453
EFT	-0.037	-0.358-0.262	0.230
WBC	0.262	0.0001-0.00015	0.004
LVEF	-0.185	-7.605-0.977	0.128
IL-6	0.097	-0.054-0.160	0.328

Adipocytes are capable of affecting cardiovascular function by releasing a variety of peptides and other molecules through autocrine, paracrine, and endocrine manners. Various studies have shown the key role of inflammation in the onset and progression of coronary atherosclerosis.[4] Increasing evidence suggests that visfatin is able to activate inflammation through activating a variety of cells such as endothelial cells, monocytes, and macrophages.[27]

Visfatin increases the expression of inflammatory cytokines such as IL-6, IL-1β, and TNF-α by activating the nuclear factor-kappa B (NF-kB) transcription factor in plaque.[15,27] In addition, various factors such as matrix metalloproteinase 9 (MMP-9), vascular cell adhesion molecule (VCAM), intercellular adhesion molecule 1 (ICAM-1), and E-Selectin, which were all reported to be induced under the influence of visfatin, are involved in endothelial dysfunction.[28] Interestingly, pro-inflammatory cytokines lead to increased visfatin expression.[29] Thus, increased levels of pro-inflammatory factors positively influence visfatin expression, and in turn, increased visfatin expression increases pro-inflammatory factors in plaque inflammatory medium. The association between CAD severity and serum visfatin levels based on the Gencini score in the present study, at least in part, reflects the exacerbation of inflammation under atherosclerotic conditions. Although the results of our study were consistent with the findings of previous studies,[17,30] there are no reports on the association of serum visfatin level with echocardiographic findings, particularly EFT in patients with AMI and SAP. Despite evidence of a significant association between visfatin and CAD severity in the present study, Choi et al. did not find such an association probably due to the small sample size of their study.[31]

Echocardiographic EFT was reported to be

indicative of the accumulation of visceral fat within the abdomen.[25] Previous studies showed that subjects with high WHR have high EFT.[24] Human studies have reported an association between EFT and cardiovascular risk factors such as metabolic syndrome, LDL-C, high insulin resistance, and inflammatory markers.[32] In fact, EFT acts as an endocrine and paracrine site for cytokines, and it has been shown that a close relationship exists between EFT and the circulating levels of adipokines such as C-reactive protein (CRP), visfatin, monocyte chemoattractant protein-1 (MCP-1), and plasminogen activator inhibitor-1 (PAI-1).[33] The findings of our study also showed a correlation between visfatin levels and EFT in patients with AMI and SAP compared to the control group. Although the exact mechanism is not clear, clinical findings indicated an association between increased EFT and CAD.[34,35] It is thought that inflammatory mediators around the epicardial coronary arteries can exacerbate inflammation, create new vessels, and cause plaque instability.[36] By exacerbating inflammation in the plaque medium, inflammatory cells infiltrate into the arterial wall, causing intimal damage and coronary vasospasm.[37] However, in an inflammatory environment, EFT can also have beneficial effects in patients with CAD through induction of angiogenesis and development of collateral vessels.[36]

In addition, we found a positive association between serum visfatin and IL-6 levels. Previous studies also showed a positive association between visfatin and other inflammatory markers such as PAI-1 and MCP-1.[33] Interestingly, the association between visfatin and IL-6 level was still present after adjusting visfatin levels with age, BMI, WHR, and smoking history, thus indicating a pro-inflammatory role for visfatin in CAD conditions. Furthermore, in a study by Fadaei et al., the increased expression of visfatin in PBMCs in patients with CAD indicated the role of immune cells in the secretion of visfatin.[17] In this regard, the circulating leukocytes together with macrophages present in adipose tissue are considered to be visfatin secretors.[13] Interestingly, the analysis of regression results in the present study showed that serum visfatin levels were independently correlated with WBC counts. The influence of visfatin on immune cells function may be principally related to its enzymatic activity (NAMPT). Increased intracellular visfatin level increases the survival of lymphocyte, possibly leading to persistent inflammation in atherosclerotic environment in patients with CAD; nonetheless, to confirm such results, further studies should be conducted.[38]

The present work, for the first time, showed that visfatin levels are associated with levels of troponin-T and CK-MB. Furthermore, our data showed that visfatin levels increased with increasing Gensini score in patients with AMI and SAP, especially in the AMI patients. To the best of our knowledge, this is the first study reporting a link between serum visfatin level and CK-MB level and CAD severity based on the Gensini score and the precise mechanism underlying this association should be investigated in future studies.

The current study had several limitations. First, we did not include women in the study, and thus, did not determine the gender effect on serum visfatin and IL-6 levels and its association with the severity of the disease. Second, the sample size of our study was not large, and thus, these variables should be evaluated in a larger sample.

Conclusion

In conclusion, the current study revealed the independent association of visfatin level with WBC counts and CK-MB level in AMI and SAP patients. In addition, our results presented a relationship between visfatin level and EFT, IL-6 level, troponin-T level, Gensini score, and LVEF. Although this study does not show the causal link between visfatin and CAD in patients with AMI, it suggests a role for visfatin in CAD. It is recommended that adipocytokines be considered both systemically and locally in the pathophysiology of patients with CAD.

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Conflict of Interests

Authors have no conflict of interests.

Authors' Contribution

MRA and LA: Literature search, Proposal writing, Data collection, Analysis of data, Interpretation of data, Manuscript preparation, Review of manuscript

HD, AN, BZ and SM: Data collection, Analysis

of data, Interpretation of data, Review of manuscript

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