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Visfatin as marker of isolated coronary artery ectasia and its severity

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ABSTRACT

Several studies have demonstrated the relationship between visfatin and increased risk of diseases caused by inflammation, however, the relationship between visfatin and coronary artery ectasia (CAE) is still unknown. The aim of our study is to investigate the association between serum visfatin with presence of coronary ectasia and its severity. We enrolled 85 individuals including 35 CAE patients (mean age: 58.40 ± 9.82 years) and 50 control persons (mean age: 53.24 ± 8.81 years). These participants underwent some biochemical tests including visfatin, fasting blood glucose and lipid profiles. In univariate analysis, the serum level of visfatin was significantly associated with ectasia in all patients with CAE and CAD coexisting with CAE groups, but a trend toward significance in isolated CAE group. In multivariate analysis, visfatin showed independently significant association with presence of ectasia in all patients with ectasia and in CAD coexisting with ectasia groups, but not significant in isolated CAE group. Visfatin was also independently associated with severity of ectasia according to MARKIS classification. We conclude that visfatin independently can be the useful predictor for the presence and severity of coronary ectasia.

1. Introduction

Coronary artery ectasia (CAE) has been considered as localized or diffuse dilation of the coronary arteries exceeding the 1.5 time of normal adjacent segment in coronary angiography [1]. In general, CAE is proposed to be a different form of vascular remodeling in response to atherosclerosis; however, the underlying mechanisms responsible for ectasia formation are not clear [2]. Over the past few years, the investigation on pathophysiology and risk factors of coronary artery ectasia has been raised. Although some underlying etiologies such as microvascular abnormality and widespread atherosclerosis of the coronary arteries have been proposed, but the exact pathophysiological mechanism of this phenomenon remains unclear [3,4]. Several studies elucidated the role of inflammatory processes such as atherosclerosis on pathophysiology of CAE and introduced various prognostic indicators of its presence and severity [3,4]. Additionally, there is an association between inflammatory markers such as hs-CRP, endocan, interleukin-6 and white blood cell, and development of CAE [5,3,4]. However, more research on introducing newly reliable markers to early diagnosis is still necessary. The inflammatory cytokine visfatin, a newly discovered adipocyte hormone, plays a key role in delayed neutrophil apoptosis in sepsis. It is highly enriched in the visceral fat of both humans and mice, and its plasma levels increase during the development of obesity [6] as well as being elevated in patients with type 2 diabetes, suggesting that measurement of plasma visfatin can be a useful tool for understanding metabolic diseases [7,8]. Higher level of visfatin is also associated with metabolite disturbances such as reduction in large High-density lipoprotein (HDL) particles and elevation of small dense low-density lipoprotein cholesterol (sdLDL-C), blood pressure and hs-CRP [9]. There is also a direct relationship between higher level of visfatin and cardiac enzymes, indicating that this adipokine might be a marker of increased cardiovascular risk [10]. There is also evidence for association between CAE and slow coronary flow (SCF) [11]. Ucguna et al. [12] found that visfatin and omentin may play a role in the pathogenesis of SCF, but the relationship between plasma levels of these adipocytokines and CAE has not been investigated. According to the role of inflammatory conditions in pathophysiology of CAE, we decided to investigate the relationship between visfatin, as a known inflammatory marker, and the presence and severity of CAE.

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Table 1
Demographic and labaratory characteristics of patients with coronary artery ectasia and control group.

	Isolated CAE N = 21	CAD + CAE N = 14	Normal N = 50	P value
Age (years)	58.30 ± 9.60	58.57 ± 10.52	53.24 ± 8.81	0.047*
Sex (%)				< 0.0001
Male	16(76.2%)	12(85.7%)	17(34%)	
female	5(23.8%)	2(14.3%)	33(66%)	
Smoking (%)				0.106
Never	16(76.2%)	7(50%)	38(76%)	
Former	4(19%)	2(14.3%)	4(8%)	
current	1(4.8%)	5(35.7%)	8(16%)	
Height (cm)	167.33 ± 8.97	171.71 ± 8.34	161.57 ± 8.09	< 0.0001
Weight (kg)	86.90 ± 13.51	88.07 ± 10.71	72.96 ± 9.70	< 0.0001
BMI (kg/m^2)	31.00 ± 4.00	30.00 ± 4.20	28.09 ± 4.16	0.020
Waist (cm)	101.77 ± 17.01	102.00 ± 11.30	101.45 ± 8.16	0.985
DM (%)	5 (23.8%)	5 (35.7%)	4 (8%)	0.027
HLP (%)	14 (66.7%)	6 (42.9%)	40 (80%)	0.024
FH (%)	5 (23.8%)	7 (50%)	12 (24%)	0.141
Visfatin (ng/ml)	5.30 ± 3.33	6.53 ± 4.11	3.17 ± 2.72	0.001
FBS (mg/dl)	99.00 (80.00–263.00)	102.50 (81.00–199.00)	104.00 (83.00–125.00)	0.718
LDL-cholesterol (mg/dl)	113.9048 ± 36.01	93.50 ± 31.05	118.40 ± 35.20	0.065
HDL-cholesterol (mg/dl)	41.33 ± 8.75	36.93 ± 5.62	46.63 ± 8.11	< 0.0001
TG (mg/dl)	114.00 (63.00–560.00)	95.00 (50.00–181.00)	130.00 (42.00–222.00)	0.015
TCHOL (mg/dl)	176.33 ± 46.37	145.86 ± 33.01	190.12 ± 45.15	0.005

Data are mean ± standard deviation or median (inter-quartile range) or frequency (prevalence rates).
CAD, coronary artery disease; CAE, coronary artery ectasia; BMI, Body mass index; HTN, hypertension; DM, diabetes mellitus; HLP, hyperlipidemia; FH, familial history; FBS, fasting blood sugar; LDL, low density lipoprotein; HDL, high density lipoprotein; TG, triglyceride; TCHOL, total cholesterol.
* The P-values between isolated CAE and CAD + CAE groups was > 0.05.

2. Methods

2.1. Study population

A total of 85 participants recruited from who were subjected to diagnostic coronary angiography due to suspected myocardial ischemia who were admitted to Tehran heart center. CAE was measured as 1.5 fold dilation of coronary artery lumen than that of normal diameter without stenosis [13,14]. Isolated CAE was defined as coronary artery ectasia without significant coronary stenosis. All participants gave their informed consent and the study protocol was approved by the institutional ethics committee.

The exclusion criteria were history of myocardial infarction (MI) in the past three months, consumption of several drugs including immunosuppressive drugs in past 1 year, chronic alcohol consumption, history of cancer, rheumatoid arthritis, systemic lupus erythematosus, hepatitis B or C virus, inflammatory bowel disease and history of previous percutaneous coronary intervention (PCI) and Coronary artery bypass grafting (CABG).

2.2. Assessment of risk factors and demographic data

Demographic data and some information about coronary artery risk factors were recorded. Anthropometric indices including weight, height and waist were measured and Body mass index (BMI) calculated by dividing weight (kg) by the square of height (m^2).

Diabetes (DM) was defined as fasting blood sugar ≥126 mg/dl [7.0 mmol/l] or HbA1c ≥ 6.5% [15]. Hypertension (HTN) was defined as blood pressure of at least 140/90 or taking antihypertensive agents [16]. Hyperlipidemia (HLP) was defined as fasting triglyceride levels > 150 mg/dl (1.7 mmol/l) or total cholesterol > 200 mg/dl (5.2 mmol/l) or taking lipid lowering treatment [17].

2.3. Laboratory measurements

Blood samples were collected following a 12 h overnight fast. Blood sample of patients were collected from the antecubital vein into EDTA-treated and plain tubes and analyzed for fasting blood sugar (FBS), low-density lipoprotein (LDL), High-density lipoprotein (HDL), Triglycerides (TG) and Total cholesterol using enzymatic methods. Serum visfatin was measured using a visfatin enzyme immunoassay (EIA) kit (Human Visfatin ELISA Kit, AdipoGen Pharmaceuticals, Belmont and Seoul Korea). The intra-assay and interassay coefficients of variance of this kit were less than 4.3% and 7.5%, respectively.

2.4. Coronary angiography assessment

Coronary angiography was carried and analyzed by experienced cardiologists, then based on the MARKIS categorization, patients classified into four types of ectasia from the point of severity. Type 1 was defined as diffuse ectasia of two or three vessels, Type 2 as diffuse disease in one vessel and localized disease in another vessel, type 3 as diffuse ectasia of one vessel only and type 4 as localized or segmental ectasia [18]. Patients with type 1 and 2 were considered as ectasia groups in our study.

2.5. Statistical analysis

Data analysis was performed using SPSS (version 16.0). Normality of distribution was assayed using Kolmogorov-Smirnov test. Continues (scale) variable with and without Normal distribution expressed as mean ± standard deviation and median and interquartile range (IQR), respectively. Normal distribution data were compared with Analysis of variance (ANOVA) test followed by post hoc comparison performed by Scheffe's test and not normally distribution with Mann-Whitney U and Kruskal-Wallis tests. Categorical variables were shown as percentages and compared with Cramer's v test. Pearson test was used to identify the correlation between serum visfatin and isolated CAE. Multivariate logistic regression and linear regression analysis of values was utilized to determine the predictive value of serum visfatin for the presence and severity of CAE. The Receiver Operating Characteristic (ROC) curve was performed and the optimal cut-off point of serum visfatin was obtained by Youden formule. P values ≤ 0.05 were considered significant.

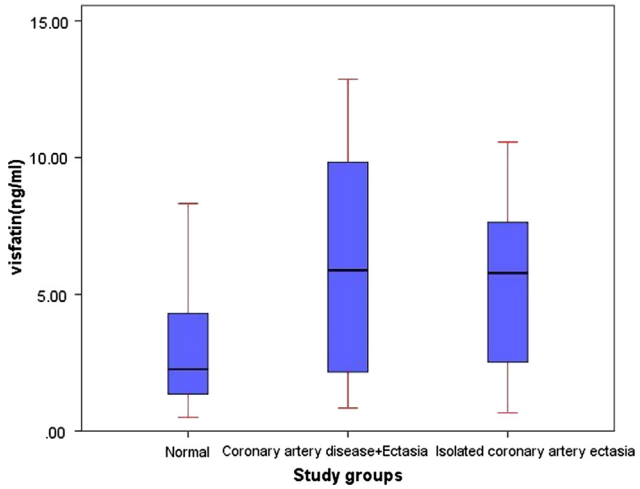

Fig. 1. Serum visfatin level in study groups. Serum level of visfatin was significantly higher in both ectatic patients (isolated CAE and CAD with CAE) than those of the control group (p: 0.037 and p: 0.003; respectively). There was no significant difference between ectasia groups ($p > 0.05$). CAD: coronary artery disease; CAE: coronary artery ectasia.

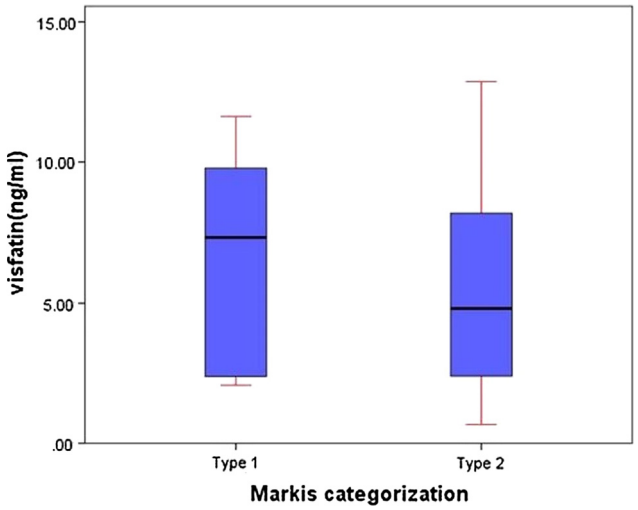

Fig. 2. Serum visfatin level in different categories of coronary artery ectasia according to Markis system. Patients with type 2 ectasia formed the majority of patients (n: 21, 77.1%).however, the mean value of visfatin (black line inside the box) in type 1 ectasia was higher than that in type 2 ectasia.

3. Results

3.1. Demographic, clinical and laboratory characteristics of subjects

Demographic, clinical and Laboratory characteristics of subjects were summarized in Table 1. We enrolled 85 persons and categorized them into three groups; 21 patients with isolated CAE, 14 patients with coronary artery disease (CAD) coexisting with CAE and 50 normal subjects which considered as control group. There was significant difference among the three groups investigated regarding the sex distribution and age ($p < 0.0001$ and p: 0.047, respectively).

Analysis of variance of serum visfatin showed significant difference among three groups (p: 0.001) (Fig. 1). In post hoc test the mean difference of both isolated ectasia group and CAD coexisting with CAE group with normal groups were significant (p: 0.037 and p: 0.003; respectively), but there was no significant difference between ectasia groups with or without accompanying CAD ($p > 0.05$).

3.2. Angiographic characteristics of CAE and CAD with ectasia groups

Based on Markis classification, patients with type 2 ectasia formed the majority of patients (n: 21, 77.1%), followed by Type 1 which includes at least two main involved diffuse artery (n: 14, 22.9%). Serum level of visfatin in both types of ectatic patients was shown in Fig. 2.

3.3. Correlation analyses of factors relating to coronary ectasia

There was significant correlation between age (r: 0.268, p: 0.013), and BMI (r: 0.290, p: 0.007) with the presence of ectasia in all patients with CAE. Univariate correlation analysis in different groups of ectasia was summarized in Table 2.

Serum visfatin was significantly associated with ectasia regardless of having accompanying CAD (r: 0.383, $p < 0.001$) and with CAD coexisting with CAE group (r: 0.301, p: 0.005), but in isolated CAE group showed a trend toward significance (r: 0.180, p: 0.098).

3.4. Multivariate regression analysis for assessment of presence and severity of ectasia

Results of multivariate logistic regression analysis were summarized in Table 3; In first model which adjusted for sex and age, serum visfatin was significantly independent marker of ectasia in all patients with CAE and CAD coexisting with CAE groups (OR: 1.250; %95 CI: 1.058–1.478, p: 0.009 and OR: 1.201; %95 CI: 1.009–1.430, p: 0.040; respectively) but not in isolated CAE group (p value < 0.05). In second model which adjusted for sex, age, HLP, HTN and DM, similarly visfatin was a significant predictor of ectasia in all patients with CAE and CAD with CAE groups (OR: 1.294; %95 CI: 1.036–1.617, p: 0.023 and OR: 1.251; %95

Table 2
Univariate correlation analysis of factors in patients with coronary artery ectasia.

	All patients with CAE N = 35		Isolated CAE N = 21		CAD coexisting with CAE N = 14	
	r	p value	r	p value	r	P value
Visfatin (ng/ml)	0.383	0.000	0.180	0.098	0.301	0.005
HDL-cholesterol (mg/dl)	−0.401	0.000	−0.159	0.143	−0.348	0.001
TG (mg/dl)	−0.088	0.419	0.070	0.520	−0.199	0.066
TCHOL (mg/dl)	−0.278	0.009	−0.040	0.716	−0.324	0.002
LDL-cholesterol (mg/dl)	−0.176	0.104	0.006	0.956	−0.247	0.022
Age (years)	0.268	0.013	0.177	0.106	0.150	0.170
Height (cm)	0.406	0.000	0.169	0.120	0.343	0.001
Weight (kg)	0.552	0.000	0.358	0.001	0.318	0.003
BMI ($kg/m^{2)}$	0.290	0.007	0.252	0.019	0.093	0.396

CAD, coronary artery disease; CAE, coronary artery ectasia; HDL, high density lipoprotein; LDL, low density lipoprotein; TG, triglyceride; TCHOL, total cholesterol; BMI, body mass index.

Table 3
Multivariate correlation analysis of related factors in patients with coronary artery ectasia.

	Model1		Model 2	
Visfatin(ng/ml)	OR (95% CI)	P value	OR (95% CI)	P value
All patients with ectasia	1.250 (1.058–1.478)	0.009	1.294 (1.036–1.617)	0.023
CAD with ectasia	1.201 (1.009–1.430)	0.040	1.251 (1.006–1.556)	0.044
Isolated ectasia	1.082 (0.932–1.256)	0.298	1.048 (0.894–1.228)	0.566

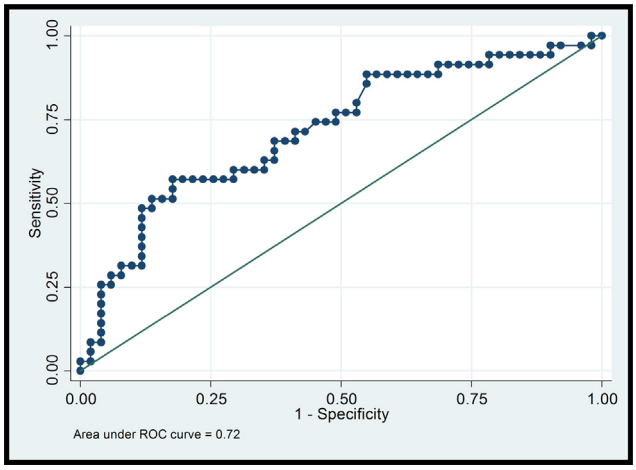

Fig. 3. Roc analysis to determine the association between coronary artery ectasia and visfatin. Cut-off value of > 4.725 ng/ml demonstrated a sensitivity of 57% and a specificity of 82% (area under the curve: 0.72, p: 0.001, %95 CI: 0.60–0.83). ROC: receiver operating characteristic; CI: confidence interval.

CI: 1.006–1.556, p: 0.044), but not in isolated CAE group (p value: 0.566).

Model 1: adjusted for age and sex
Model 2: adjusted for age, sex, HLP, HTN and DM

In multivariate linear regression for MARKIS score in two mentioned models, Visfatin was significantly associated with severity of ectasia in both model 1 (β: 0.229, p: 0.015) and model 2 (β: 0.160, p: 0.047).

3.5. Roc analysis to determine the optimal cut-off of visfatin for prediction of ectasia

The area under the Roc curve of visfatin for prediction of Ectasia in all patients was 0.72 (p: 0.001, %95 CI: 0.60–0.83) (Fig. 3). A visfatin value > 4.725 had a sensitivity of %57 and a specificity of %82 for prediction of Ectasia.

4. Discussion

Our study demonstrated that higher serum level of visfatin was significantly correlated with the presence of ectasia in CAD coexisting with CAE group and had a trend toward significance in isolated CAE group. Furthermore, we concluded that visfatin is an independent marker for severity of coronary ectasia in both isolated CAE and CAD coexisting with CAE groups. To the best of our knowledge, this is the first study about the association between serum visfatin and CAE.

The exact pathogenesis of ectasia has not already been identified, although its coexistence with atherosclerosis and inflammatory processes has been introduced. So, several studies have been designed about the role of atherosclerosis and inflammatory markers in predicting ectasia [4,19]. In addition, Higher mortality in patients who suffering from CAD with simultaneous CAE in comprising with patients without ectasia (non-CAE) [20] is enforcement for researchers to identify useful markers for prediction of CAE.

There are several studies about the relationship between inflammatory indices and ectasia. Demir et al. illustrated that higher serum level of hs-CRP, uric acid and mean platelet volume (MPV), as well lower serum level of bilirubin, which are known as indicators of atherosclerosis, correlated with ectasia[21,22,5]. Huang et al. showed that alkaline phosphatase, been recognized to be raised at inflammatory status, is an independent marker of isolated CAE [23]. Turan et al. showed the significant association between Plasma Endocan, which previously has been introduced as marker of inflammation and endothelial dysfunction, and presence of ectasia and its severity [4].

Visfatin is known as an adipocytokine and stimulant for increasing the level of inflammatory cytokines including Interleukin 1 beta, Tumor necrosis factor alpha, and especially Interleukin 6 [8,24,25]. Several studies illustrated the relationship between visfatin level and metabolic disturbances which leads to atherosclerosis, independent of well-known CAD risk factors [9,26]. In addition, increased level of serum visfatin which sequentially results to its loading in lipid-rich macrophages have been shown to be associated with plaque destabilization, determining the predictive role of visfatin in systemic inflammation and atherosclerosis [27]. There is also evidence that CAE may be associated with low coronary flow rates [11]. Ucguna et al. [12] found that visfatin level is higher in patients with low coronary flow rates, but the relationship between plasma levels of visfatin and CAE has not yet been investigated.

There are a few studies investigating the cutoff for visfatin level as a prognostic indicator in process of inflammation. However, Mean serum level of visfatin in ectasia group in our study was lower than that found in other studies investigating visfatin in inflammatory processes. Farahani et al. [28] found that a visfatin level > 7.244 ng/ml as predictor for acute myocardial infarction have a sensitivity of 70% and specificity of 75%. We showed that a visfatin level > 4.725 ng/ml had a sensitivity of %57 and a specificity of %82 for prediction of Ectasia.

The question that rises is whether higher level of visfatin in all patients with CAE and CAD coexisting with CAE groups is due to ectasia or its accompany with CAD. Our descriptive analysis shows that visfatin is significantly different between isolated CAE and control group. In addition, when we assayed visfatin as covariate for the presence of ectasia, there was a trend toward significance. Additionally, we found significant independent association between higher level of visfatin with severity of ectasia in both isolated CAE and CAD coexisting with CAE groups.

We encountered a surprising finding about the reverse relation of lipid disturbances with coronary ectasia which is in contrast to previous studies [29,30]. Lower cholesterol and triglyceride and higher HDL levels in ectasia group may be due to consumption of statins but related data for analysis was not available for us.

Limitations: This study has some limitations that are worth noting. First, because the patients enrolled in our study were candidates for coronary angiography, our findings cannot be extrapolated to the general population. Second, given the cross-sectional design of our study, the directionality of the association cannot be determined. Third, we used a single baseline measurement. We therefore cannot evaluate the effects of changes in this parameter over time. Fourth, we didn't enroll the CAD patients without ectasia, hence further investigation are needed to compare the serum level of visfatin in these patients with patients who have ectasia. Finally, on account of the observational design we cannot report or make conclusions with regard to event outcomes.

5. Conclusion

Our results reinforced the evidence that serum visfatin can be used as a marker for presence and severity of ectasia which is considered as an inflammatory statue. Further studies are suggested to clear the mechanism of this association.

Declaration of interest

The authors declare that there are no conflicts of interest.

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