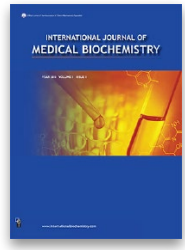
INTERNATIONAL JOURNAL OF
MEDICAL BIOCHEMISTRY

DOI: 10.14744/ijmb.2018.05925
Int J Med Biochem 2018



Research Article

Visfatin: A potential biomarker for the early diagnosis and monitoring of acute coronary syndrome

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Abstract

Objectives: Acute coronary syndrome (ACS) is a major cause of mortality and morbidity worldwide, thus early diagnosis is very important. The most common cause of ACS is the rupture of vulnerable atherosclerotic plaque in the coronary artery in which inflammation plays a key role. The aim of the present study is to investigate visfatin, as a proinflammatory biomarker in the early diagnosis and monitoring of ACS and to compare visfatin's relationship with troponin T, tumor necrosis factor-alpha (TNF-α), and creatine kinase-MB (CK-MB).

Methods: Sixty ACS patients and thirty control subjects were recruited to this study. From controls one, from ACS patients three blood samples were obtained at intervals 0-6 (T0), 6-12 (T1) and 12-24 (T2) hours from the start of the chest pain. Serum visfatin, TNF-α, troponin T and CK-MB were assessed. Visfatin and TNF-α levels were assessed by ELISA, troponin-T by chemiluminescence and CK-MB by enzymatic methods.

Results: Serum TNF-α, troponin T and CK-MB levels in T0 blood samples were statistically significantly higher in ACS patients compared to controls ($p=0.004$, $p<0.001$, $p<0.001$ respectively). We found a significant positive correlation between visfatin and troponin T ($r=0.290$,$p=0.007$) in T0. Visfatin concentrations were decreased in T0, T1 and T2 samples [4.01±6.23ng/ml, 1.80±3.47 ng/ml and 1.72±2.67ng/ml, ($p=0.005$) respectively, T0>(T1=T2)].

Conclusion: Visfatin shows a significant positive correlation with troponin T. Visfatin did not demonstrate a rise and fall pattern like the standart biomarkers in terms of monitoring of ACS patients evolution, because it shows a significant decrease after first 6 hours. Although visfatin has no superiority to troponin, since its increase is correlated, its efficiency in a multimarker panel needs investigation. The role of visfatin in the early phase pathophysiological mechanisms needs to be elucidated.

Keywords: Acute coronary syndrome, adipokines, troponin T, tumor necrosis factor-alpha, visfatin

Coronary artery disease, which is the most common type of heart disease, is the leading cause of death for both sexes. Therefore, early diagnosis is very crucial [1]. According to the statistics, the annual direct and indirect costs are about $310 billion in USA in 2009 [2].

Acute coronary syndrome (ACS), defined as a group of symptoms originated from the occlusion of coronary arteries, ranges from ST-segment elevated myocardial infarction (STEMI), non ST-segment elevation (NSTEMI) to unstable angina pectoris (UAP) [3]. Acute coronary syndromes occur with atherosclerotic plaque rupture or erosion, then thrombus formation and arterial occlusion. Inflammation is associated with all forms of atherosclerotic plaques [3, 4].

Adipose tissue secretes several adipocytokines; such as visfatin, leptin, adiponectin, omentin-1 and tumor necrosis factor-alpha (TNF-α). These adipokines play an important role in

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Submitted Date: August 16, 2018 **Accepted Date:** September 28, 2018 **Available Online Date:** October 26, 2018
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the pathogeneses of insulin resistance, diabetes mellitus, dyslipidemia, inflammation, and atherosclerosis [5, 6]. TNF- α, a proinflammatory cytokine, a main mediator of inflammation, is predominately expressed in atherosclerotic lesions [7, 8].

Visfatin, a 52 kDa protein, is an adipokine which was originally discovered in liver, skeletal muscle and bone marrow as a growth factor for B lymphocyte precursors. It was first named pre-B-cell colony enhancing factor [9-11]. Visfatin, suggested to be an insulin-mimetic adipokine, is mainly produced in adipose tissue and macrophages. Visfatin displays a proinflammatory action and is localized in macrophage foam cells [12, 13]. According to a study, visfatin and TNF-α levels demonstrated positive correlation with radiographic progression of atherosclerosis in patients with rheumatoid arthritis [14], thus they might be useful markers for disease progression in early stages.

Biomarkers play important roles in diagnosis, risk assessment and monitoring of patients with acute coronary syndrome. Today in the early diagnosis and monitoring of ACS, troponins, creatine kinase-MB (CK-MB) and myoglobin are popular markers being used. However, the previously advocated use of myoglobin as an early marker of ACS has recently been discouraged mainly because of its poor performance compared to the precise and sensitive troponin assays [15, 16]. Investigations are continuing for the possible identification of patients with ACS to make earlier coronary intervention possible.

In the literature, there are some studies investigating serum visfatin levels in metabolic syndrome and myocardial infarction. However, to the best of our knowledge, there are not any studies investigating visfatin as a proinflammatory biomarker for monitoring acute coronary syndrome. The aim of the present study is to investigate visfatin as a biomarker in the early diagnosis and monitoring of ACS and to compare its relationship with troponin T, TNF-α, and CK-MB.

Materials and Methods

Study subjects

Sixty ACS patients (Group 1) and thirty control subjects (Group 2) were recruited to this study. Thirty healthy subjects were selected among voluntary hospital staff as a control group who were age, gender and body mass index (BMI) matched with patients. This study was conducted in accordance with the Declaration of Helsinki and was approved by the local Ethics Committee of Manisa Celal Bayar University, Faculty of Medicine (approval number: 20478486-0.50.04.04). All subjects in the study supplied informed consent and answered the questionnaire prepared for their health records. The ACS patient group was selected among consecutive adults admitted to emergency department with acute chest pain. The diagnosis was established for coronary heart disease according to clinical symptoms, ECG findings, and cardiac markers, confirmed with coronary angiography performed in the cardiology department of the Manisa Celal Bayar Hospital.

All patients underwent coronary angiography by femoral access. The diagnosis of ACS was confirmed by coronary angiography in all study patients with standard methods.

Patients presenting with dyspnea after a trauma or malignancy and patients who refused to participate to the study were excluded. Other exclusion criteria's were as follows: diabetes mellitus, chronic inflammatory disease, liver disease, muscle disease, chronic renal failure and previous coronary angiography.

Sample collection

Venous blood samples of patients were collected three times, at intervals: 0-6 hour (T0), 6-12 h (T1), 12-24h (T2) after the onset of the first symptoms. Control subjects gave a single venous sample. All blood samples were collected into serum separator tubes. They were centrifuged at 3000 g for 4 min at 4°C. Sera were stored at –80°C until analysis.

Assay methods

Serum visfatin levels were assessed by enzyme-linked immunosorbent assay (ELISA) method using the Human Visfatin ELISA Kit (Alpco Diagnostics, Salem, NH, USA). The sensitivity was 30pg/mL, intra-assay coefficient of variation (%CV) was 4.31 and inter-assay % CV was 7.58. TNF-α levels were assessed by ELISA method using the commercial kit (Biosource, Europe S. A., Nivelles, Belgium). The sensitivity was 1.7 pg/mL, intra-assay and inter-assay CV were 4.4% and 7.5 %, respectively. Serum troponin T levels were determined by chemiluminescence method (Elecsys 2010, Hitachi, Japan). Serum glucose, urea, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), CK-MB, triglyceride, cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) levels were assessed on auto-analyzer (Synchron Unicel DXC 800, Beckman Coulter, Fullerton, CA, USA) with the commercial kits (Beckman Coulter, Mervue, Galway, Ireland). Body mass index (BMI) was calculated by the formula; weight (kg)/height (m)2.

Statistical analysis

The patient group consists of 60 patients and the controls are 30 persons. The 30 controls were taken for the purpose of satisfaction parametric distribution and running parametric tests.

Statistical analyzes were carried on SPSS 15.0 statistical package. Normality assessments were done by Shapiro Wilk test. Students't test and Mann-Whitney U test were used in normal and abnormal distributed data where appropriate. In repeated measurements' analyses (dependent groups' analyses) Friedman Nonparametric test was used. Post hoc nonparametric comparisons are also made by Wilcoxon test. Chi-square tests were used for the comparison of the categorical variables. Continues variables were compared by means of Pearson correlation analyses. Type 1 error was taken as 0.05 for the entire statistical comparisons.

Results

Sixty ACS patients and age, gender and BMI matched thirty control subjects were included in the study. Demographic data and routine biochemical parameters of the study groups are shown in Table 1. Results of visfatin, TNF-α, troponin T and CK-MB levels in T0 are shown in Table 2. Visfatin levels are not statistically higher in ACS patients than the controls in T0 (4.01±6.23 vs. 1.46±1.18, p=0.128). Changes of visfatin levels, TNF-α, troponin T and CK-MB levels in T0, T1, and T2 are present in Table 3. Visfatin levels were highest in T0. T1 and T2 levels were statistically significantly lower than T0. There isn't any significant difference between T1 and T2 in visfatin levels. Correlations between visfatin and troponin T, TNF-α, CK-MB in T0 are shown in Table 4. In T0, positive correlations were observed between visfatin and troponin T (r=+0.290, p=0.007).

In the ACS group, 63.3% (n=38) were diagnosed with STEMI, 21.7% (n=13) diagnosed with UAP, and 15.0% (n=9) diagnosed with NSTEMI. There were no statistically significant differences in visfatin levels between controls and STEMI, NSTEMI and UAP (Data not shown).

Table 1. Demographic data and routine biochemical parameters of the study groups

	ACS (n=60) mean±SD	Control (n=30) mean±SD	p value
Age (year)	61.50±13.53	60.40±5.03	0.669*
Sex			
male (%)	46 (76.7)	22 (73.3)	0.729**
female (%)	14 (23.3)	8 (26.7)	
BMI (kg/m^2)	24.86±2.68	25.02±3.05	0.810*
Glucose (mg/dL)	100.08±10.38	96.13±12.41	0.115*
AST (U/L)	55.33±56.18	23.13±4.11	0.001***
ALT (U/L)	27.03±16.16	21.47±7.71	0.078*
LDH (U/L)	179.12±45.44	157.96±28.84	0.032*
Cholesterol (mg/dL)	178.00±50.29	177.63±25.46	0.970*
HDL-C (mg/dL)	34.56±9.78	35.66±10.10	0.619*
LDL-C (mg/dL)	118.73±34.92	115.53±20.59	0.646*
Triglyceride (mg/dL)	132.10±149.12	134.67±59.46	0.141***
Urea (mg/dL)	35.72±15.24	32.37±9.23	0.272*
Creatinine (mg/dL)	0.99±0.27	0.99±0.18	0.976*
Hypertension			
Yes (%)	32 (53.3)	17 (56.7)	0.765**
No (%)	28 (46.7)	13 (43.3)	
Smoker			
Yes (%)	33 (55.0)	16 (53.3)	0.881**
No (%)	27 (45.0)	14 (46.7)	

*Student's t test
**Chi-Square test
***Mann-Whitney U test
Categorical variables are expressed as n (%)
ACS: Acute coronary syndrome; BMI: Body mass index; HDL-C: high-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase

Table 2. Data on visfatin, TNF-α, Troponin T and CK-MB in the study groups in T0*

	ACS (n=60) mean±SD	Control (n=30) mean±SD	p value
Visfatin (ng/mL)	4.01±6.23	1.46±1.18	0.128**
TNF-α (pg/mL)	12.77±6.08	9.22±2.02	0.004*
TroponinT (ng/mL)	1.74 ±3.49	0.02±0.03	<0.001**
CK-MB (U/L)	23.56±28.04	2.83±1.71	<0.001**

*Student's t test
**Mann Whitney U test
TNF-α: Tumor necrosis factor alpha; CK-MB: creatine kinase-MB

Discussion

Acute coronary syndrome is precisely the most common causes of mortality and morbidity in the world. There are four pathological mechanisms in ACS: systemic inflammation with plaque rupture, plaque rupture without systemic inflammation, erosion of plaque, and plaque without thrombus [17].

The atherosclerotic plaque is composed of both intracellular and extracellular lipid-containing vascular smooth muscle cells and inflammatory cells [3]. Excessive adipose tissue surrounding the blood vessels may cause increased amount of perivascular fat and thus may stimulate inflammatory state. The chronic state of inflammation in the adipose tissue causes increase in the secretion of proinflammatory cytokines such as interleukin 6, adiponectin and TNF-α which might also cause endothelial dysfunction [18]. Inflammation is associated with all forms of atherosclerotic plaques, both stable and unstable, whereas stable ones are characterized by chronic inflammation; unstable ones are by acute inflammation. The pathogenic role of macrophages and lymphocytes in plaque destabilization is concluded to be associated with the secretion of cytokines and lytic enzymes thus predisposing a lesion to rupture. The adipose-tissue derived circulating inflammatory markers are thus important in this process. Because pro-inflammatory cytokines and chemokines are accused of plaque rupture, anti-inflammatory therapy or immune-modulatory treatment is under investigation [4].

There are some conflicting data in the literature for TNF-α level in patients with coronary heart disease. Some studies suggest that TNF-α, being the main mediator of inflammation, is located in atherosclerotic lesions and caused progression and ruptures in atherosclerotic plaques [7, 8, 19]. In a study, TNF-α levels from the tissue of epicardial and abdominal adipose tissues were higher in patients with myocardial infarction and UAP than in controls [20] similar to our findings. Kręcki R et al. found significantly higher TNF-α levels in coronary heart disease than in the controls [21]. However, in their study in-

Table 3. Visfatin, TNF, Troponin T and CK-MB levels in T0, T1 and T2

	T0 (mean/mean rank)	T1 (mean/mean rank)	T2 (mean/mean rank)	p value*	post hoc**
Visfatin (ng/mL)	4.01±6.23/2.36	1.80±3.47/1.81	1.72±2.67/1.83	0.005	T0>(T1=T2)
TNF-α (pg/mL)	12.77±6.08/2.39	9.96±3.53/1.99	8.89±3.09/1.61	<0.001	T0>T1>T2
TnT (ng/mL)	1.74±3.49/1.61	3.11±4.48/2.21	3.56±4.19/2.18	<0.001	T0<(T1=T2)
CK-MB (U/L)	23.56±28.04/1.87	53.36±62.70/2.06	72.07±110.65/2.07	0.186	NS

*Friedman test
** Wilcoxon test
TNF-α: Tumor necrosis factor alpha; CK-MB: creatine kinase-MB
TnT: Troponin T

Table 4. Correlations between Visfatin and TNF, Troponin T, CK-MB in T0*

	Visfatin	
	r=	p=
Troponin T	0.290	0.007**
TNF-α	-0.089	0.429
CK-MB	0.195	0.070

*Pearson correlation test
**p<0.01
TNF-α: Tumor necrosis factor alpha; CK-MB: creatine kinase-MB

cluding ischemic coronary patients and controls, Djordjevic VB et al. did not find a statistically significant difference between the TNF-α levels of the patients and the controls [22]. Torre-Amione et al. reported that TNF-α concentrations were significantly increased in patients with ischemic heart disease [23]. It is suggested that TNF-α is an important contributor to cardiomyocyte death post myocardial infarction [24]. In our study, TNF- α levels are significantly higher than the controls in the first 6 hours due to inflammation in accordance with the literature. However, TNF-α levels were significantly decreased after first 6 hours in T1. Therefore, we believe that the use of TNF-α in the monitoring of ACS patient would not be beneficial.

Adipose tissue is an endocrine organ which can secrete adipocytokines like visfatin, TNF-α, adiponectin, leptin, and resistin [25]. In obese subjects, macrophages in white adipose tissue were shown to be responsible for production of visfatin more than adipocytes [26]. Visfatin is also released by the adipose tissue of the epicardium and may influence cardiac activity. A study demonstrated that visfatin levels in abdominal and epicardial adipose tissue were found to be significantly increased in coronary artery disease patients in comparison to the controls [27]. Moreover the serum visfatin levels were positively related with fat thickness of the epicardium. Therefore visfatin is considered to be a serious risk factor for the coronary artery disease patients [27].

Visfatin has proinflammatory activity in human monocytes and vascular endothelial cells [28, 29]. Visfatin in the literature is expressed to activate endothelial nitric oxide synthase and then improves the endothelial cell function via angiogenesis [30]. Essentially visfatin was found to be a significant protective protein in endothelial cells, by prohibiting endothelial cells from aging and injury [31]. Visfatin can be linked with inflammatory actions of endothelial cells [32]. Visfatin exhibits an essential role in the inflammation, oxidation with possible leads to endothelial dysfunction [33].

Role of visfatin is believed to be controversial. It was shown to have a proinflammatory effect since it induced the expression of TNF- α and IL-6 in leukocytes [29] and it is called as a harmful agent because of so called proinflammatory effects in cardiovascular and metabolic disorders [20]. A meta-analysis [34] reported that in obese subjects with type 2 diabetes mellitus [35] and metabolic syndrome, elevated visfatin levels were found as risk factors for cardiovascular diseases [36]. Higher visfatin levels are related to high blood pressure and higher levels of CRP and LDL-C [36]. There is also a direct correlation between higher visfatin levels and cardiac enzymes. Thus, Lu et al. suggests that visfatin might be a marker of increased cardiovascular risk [37]. Contrary to those findings, the potential beneficial effects of visfatin were determined by different researchers. Smith et al. showed that visfatin levels had a positive correlation with beneficial lipoproteins HDL-C and Apo-A1 [38]. In another study, Lim et al. observed a reduction in the infarct size with a treatment by visfatin in murine model [39]. In another study the visfatin levels are found to be upregulated in rat heart tissue by wine consumption possibly by the cardioprotective components, which are hydroxytyrosol resveratrol and tyrosol, [40] implying that visfatin can be cardioprotective. Hsu et al. suggested that visfatin can protect against myocardial infarction via coordinating autophagy of cardiomyocytes [41]. Contrary to these, in a study by Choi et al. lipocalin-2 and visfatin levels were evaluated in coronary heart disease patients. They found that visfatin levels were not different among coronary artery disease and controls [42].

Visfatin, known to be an inflammatory protein coupled with plaque destabilization and ACS [12, 43]. Chiu et al. showed visfatin in leukocytes isolated from blood of patients with acute STEMI, and from macrophages isolated from coronary ruptured plaques histochemically [44]. They suggested that vis-

fatin might play a role in atherosclerotic plaque rupture. Similar to their findings, in our study, in patients with ACS, visfatin levels were found to be elevated in the first six hours after the onset of symptoms, for which Chiu et al explained it with an accelerated monocyte and neutrophil yielding correlation of visfatin levels. Nevertheless Yang et al. suggest that elevated plasma visfatin levels increase MI risk and that visfatin may be a promising biomarker for MI [45]. In accordance with the researchers, Lu et al. found that plasma visfatin levels were significantly higher in myocardial infarction and the elevated visfatin levels correlate with higher cardiac enzymes levels. They suggest that increased plasma visfatin may be strictly linked to the myocardial damage [38]. However, the mechanism of visfatin in cardiovascular diseases still needs to be elucidated. In our study, visfatin levels are not statistically significantly increased in the ACS patients than healthy subjects in first 6 hours. Moreover, there is a positive correlation between visfatin and troponin T in the first 6 hours. However, according to our statistical data, visfatin is not superior to classic cardiac biomarker such as troponin in early diagnosis and monitoring of ACS. We think that, the role of the visfatin in the early period of ACS can be better understood by the detection of changes in visfatin levels in first 6 hours of ACS. Due to both plaque destabilization and cardioprotective effects, visfatin may be a dual effective adipokine such as adiponectin. We believe that further studies are needed for the complete elucidation of the pathophysiological mechanisms of visfatin.

Recently, the goal of physicians is to use clinical markers to identify patients at risk for ACS. Wang et al. suggested that visfatin may be an independent risk factor of coronary heart disease and increased levels of visfatin may be involved in the occurrence and development of coronary heart disease [46]. The Jupiter trial demonstrated that, rosuvastatin used daily 20 mg significantly lowered cardiovascular mortality in low- and/or intermediate-risk patients with LDL-cholesterol levels lower than 130 mg/dL and over 2 mg/L hs-CRP levels. However, no single biomarker can sufficiently predict the risk for coronary artery disease [47]. For example, multimarker risk assessment tools are better than LDL alone [48]. We think that, since it increases in the early period of ACS, visfatin may be a helpful parameter added to the multimarker panel for primer protection of low and moderate risk patients.

Visfatin was first investigated in our study as a biomarker for the monitoring of acute coronary syndrome. Classical cardiac markers such as troponins and CK-MB have been used in diagnosis and monitoring of patients with ACS. Cardiac troponins have shown to be advantageous by being a powerful risk assessment tool, having greater specificity and sensitivity, making detection of recent myocardial infarction up to 2 weeks after onset possible, and being useful for selection of therapy. However, the low sensitivity in early period of myocardial infarction and requirements of repeated measurements in 8-12 h, when results are negative, are disadvantages of the troponins (49). In our study, increased visfatin levels in early period of ACS show a decrease after first 6 hours. After first 12 hour period no significant difference was found in visfatin levels between T1 and T2 levels. The recent development of a high-sensitive cardiac troponin T assay permits detection of very low levels of troponin T. Using the high-sensitive cardiac troponin T assay improves the overall diagnostic effectivity in patients with uncertain acute myocardial infarction, while a negative result also has a high negative predictive value. In emergency patients with acute myocardial infarction symptoms, the high-sensitive cardiac troponin T significantly improves the early diagnosis of acute myocardial infarction in comparison to the standard troponin T assay [50].

In conclusion; visfatin shows a significant positive correlation with troponin-T. Increased visfatin levels show a significant decrease after the first 6 hours. Therefore, visfatin cannot be a good biomarker in the monitoring of ACS patients. Although visfatin has no superiority to troponins at early diagnosis and monitoring of ACS, since its increase is correlated to troponin T, it could be an addition to the multimarker panel in the first 6 hours. In order to understand the role of visfatin in early period of ACS, the pathophysiological mechanisms have to be elucidated.

Ethics Committee Approval: The medical ethics committee of Manisa Celal Bayar University Medical Faculty approved the study. (Approval number: 20478486-0.50.04.04).

Conflict of interest: None declared.

Fundings: This article was supported by a grant from the Scientific Research Projects Unit of Manisa Celal Bayar University (Project No: 2006-124).

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept – Y.G., O.B.; Design – Y.G., O.B.; Supervision – Y.G., O.B., C.U.; Fundings - Y.G., O.U., G.D.H.; Materials – Y.G., O.B., O.U., M.A.; Data collection &/or processing – Y.G., O.U., M.A., G.D.H.; Analysis and/or interpretation – Y.G., G.D.H., S.C., O.B., C.U.; Literature search – Y.G., S.C., M.A.; Writing – Y.G., S.C.; Critical review – Y.G., O.B., C.U.

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