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The relationship between visfatin and cardiac markers on induced myocardial infarction in rats

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ABSTRACT

Myocardial infarction (MI) is one of the most important reason of mortality into worldwide. Visfatin is a novel adipokine which was reported increased in metabolic syndrome and obesity. Moreover, it is known that visfatin increases in aterosclerotic endotelial dysfunction. In our study we want to demonstrate how visfatin changes in isoproterenol (ISO) induced MI. Rats were allocated into 4 groups in which each group included 6 rats in this study. 200 mg/kg ISO was administered into rats except control group to induce MI. I. and II. Group rats in 6th hour, III. Group rats in 24th hour and IV. Group rats in 7th day were decapitated. Visfatin was searched in cardiac tissues of all groups by immunohistochemistry stainning. Visfatin and cardiac markers' levels were measured in serum samples. Serum visfatin levels gradually increased in 6th and 24th hour in MI rats compared to controls. In 7th day visfatin levels decreased to control levels. These changes correlated with serum troponin T levels. These findings were supported by immunohistochemistry stainning of visfatin in cardiac tissues. It has been shown that visfatin could be useful in diagnosing MI and may be a biomarker for cardiac ischemia because of increasing in systemic circulation and cardiac tissues in MI like troponins.

1. Introduction

Myocardial infarction is one of the major causes of mortality in worldwide. Although the myocardial infarction is considered a problem of developed societies, it is also increasing in developing societies [1]. However, thanks to the improvements in diagnosis and treatment of MI, a significant reduction in mortality was achieved [2]. The importance of early diagnosis in MI has increased development of cardiac markers. Nowadays, troponins are used as gold standard for MI because of their high specificity among cardiac markers [3]. Therefore, cardiac troponins appear to be an absolutely desired test when MI is considered [4]. In addition to troponins, creatine kinase MB (CK-MB), lactate dehydrogenase (LDH) and aspartate aminotransferase (AST) are used as cardiac markers [5]. The specificity of troponins in cardiac tissue is very high and troponin levels are proportional to the size of the infarct area [6]. However, there are studies to discover new cardiac markers other than troponins in order to make early diagnosis and prevent unnecessary admission to the hospital [7].

Adipose tissue is not just a place to store triglycerides; is an endocrine organ in which various bioactive molecules called adipokines are synthesized. Adipokines have a wide range of functions, including processes such as insulin sensitivities, homeostasis, regulation of the immune system and inflammation [8]. In 2005, visfatin, an adipokine identified by Fukuhara et al. [9], was found to be elevated in obesity and metabolic syndrome, which are among the risk factors for cardiovascular diseases [9–11]. In addition, visfatin has been shown to increase in endothelial dysfunction, an important step in the formation of atherosclerosis [12]. However, this role of visfatin in atherosclerosis has not been fully confirmed by subsequent studies [13,14]. According to the article published in 2014, 362 MI have been diagnosed and it has been shown that visfatin levels increase in MI in plasma samples taken from 322 healthy individuals [15]. In addition to circulation in MI cases, especially in ST-segment elevation MI (STEMI), visfatin levels in macrophages have also been shown to increase [16]. Our study in-

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vestigates changes in visfatin levels on rats in the experimental MI model and its association with cardiac markers.

2. Materials and methods

2.1. Animals and experimental design

All animal experiments were carried out with the approval of the Animal Ethics Committee of Firat University Medical Faculty, Elaziğ, Turkey. In our study, we used 24 Wistar Albino (8–10 week old female rats) weights of 200–210 g provided by Firat University Experimental Research Center. All rats were kept in the same environment and given the same standard rat diet, water and food intake were provided as much as possible. The experimental animals were divided into 4 groups as 6 animals in each group; group I (control), group II (6 h), group III (24 h), group IV (7th day). During the experiment no application was made to the control group. 200 mg/kg isoproterenol (Isoproterenol hydrochloride, I5627, Sigma-Aldrich Corporation St. Louis, USA) was subcutaneously administered to the rats in other groups to induce myocardial infarction. At the end of the experiment; rats in groups I and II at 6th hour, in group III rats at 24th hour and group IV rats at 7th day were decapitated under anesthesia by intraperitoneal administration of ketamine (75 mg/kg) + xylazine (10 mg/kg). After decapitation, cardiac tissues of rats were taken and stored at −80 °C until working day. The serum samples from subjects also were kept at −80 °C until the day of study.

2.2. Masson staining

Cardiac tissues from each group were fixed in a 10% formaldehyde fixative solution for 24 h and then taken to wash under tap water. The tissues washed for 24 h in tap water were then passed through routine histological series and embedded in paraffin blocks. Masson tricrom stainning was applied to 5 µm sections taken from paraffin blocks. Histological sections were evaluated by light microscope and photographed.

2.3. Immunohistochemistry

The avidin-biotin-peroxidase complex method was used to determine visfatin immunoreactivity in cardiac tissues [17]. 5–6 µm sections were taken from the paraffin blocks into the lams. Deparaffinized tissues were passed through graded alcohol series and boiled in microwave (750 W) for first 7 min and then second 5 min at pH: 6 in citrate buffer solution for antigenicity. After boiling, it was left at room temperature for about 20 min. After washing by 3 times for 5 min each with PBS (Phosphate Buffered Saline, P4417, Sigma-Aldrich, USA), the tissue was incubated for 5 min with hydrogen peroxide block solution to prevent endogenous peroxidase activity (Hydrogen Peroxide Block, TA-125-HP, Lab Vision Corporation, USA). These tissues were washed with PBS by 3 times for 5 min each. Then, a solution of Ultra V Block (TA-125-UB, Lab Vision Corporation, USA) was applied for 5 min to prevent background paintings. Then incubated with NAMPT (Visfatin) primary antibody (NAMPT primary antibody, EAP0059, Elabscience Biotechnology, China) diluted 1/50 at room temperature for 60 min. The tissues were incubated at room temperature for 30 min in a humidified environment with a secondary antibody (Biotinylated Goat Anti- Poli-Antigen (anti-mouse/rabbit IgG), TP-125-BN, Lab Vision Corporation, USA) after washing with PBS by 3 times for 5 min each after application of the primer antibody. The tissues were washed with PBS by 3 times for 5 min each after the application of the secondary antibody and incubated at room temperature for 30 min with Streptavidin Peroxidase (TS-125-HR, Lab Vision Corporation, USA) for 30 min, then taken in PBS. Positive signals were seen by incubating the sections with the chromogen 3-amino-9-ethylcarbazole(AEC) substrate + AEC chromogen (AEC Substrate, TA-015 ve HAS, AEC Chromogen, TA-002-HAC, Lab Vision Corporation, USA), while washed with PBS. Mayer's hematoxylin-counterstained tissue was washed with PBS and distilled water and covered with appropriate closure solution (Large Volume Vision Mount, TA-125-UG, Lab Vision Corporation, USA). Histological sections were evaluated by light microscope and then photographed. In the evaluation of immunohistochemical stainning, the prevalence of immunoreactivity (0, 1: < 25%, 0, 4: 26–50%, 0, 6: 51–75%, 0, 9: 76–100%) and intensity from 0 to 3 were semiquantitatively formed histological scores.

2.4. Serological analysis

Troponin T measurements were performed on a Roche Elecsys 2010 (Roche Diagnostics GmbH, Mannheim, Germany) device by electrochemiluminescence method; Measurements of CK-MB, LDH and AST were performed spectrophotometrically on a Beckman Coulter AU680 (Beckman Coulter K. Tokyo, Japan) autoanalyser and CRP measurements were nephelometrically performed on Immage 800 (Beckman Coulter Inc., USA).

Serum visfatin levels were measured with the Rat Visfatin ELISA Kit (Catalog No. E-EL-R1067, Elabscience Biotechnology Co., Ltd., China). The substances in the kit, the patients and controls serum samples were allowed to stand at room temperature for 30 min. Serums were diluted 50-fold and the results were calculated accordingly.

2.5. Statistical analysis

The data obtained in the study were given as mean ± standard deviation. Kruskal Wallis one way variance analysis test was used to compare the parameters between the groups. Mann Whitney-*U* test was used in the binary comparisons between the groups. The Spearman correlation test was used to examine the relationship between the groups' parameters. Regression analysis was also conducted to determine the power of the relationship between groups and to model it mathematically. All statistical analyzes were performed using the SPSS version 21.0 (SPSS Inc., Chicago, IL) program.

3. Results

When serum visfatin levels of control and MI groups were evaluated; visfatin levels were observed to increase at 6th and 24th hours after MI according to the control group. This increase was statistically significant between MI groups and the control group ($p < 0.05$). On the seventh day, visfatin levels decreased to control levels. There was no statistically significant difference between control and 7th day levels (see Table 1).

When troponin T levels of control and MI groups are compared; troponin levels were increased in groups 6 and 24 after MI according to the control group. This increase was statistically significant between MI groups and the control group ($p < 0.05$). On the seventh day, visfatin levels decreased to control levels. There was no statistically significant difference between control and 7th day levels. The changes in troponin levels in our study are consistent with previous studies [17]. LDH, AST, CK-MB and CRP levels were also investigated in our study.

Statistically significant positive correlations were found between levels of visfatin in the groups and levels of Troponin T (r: 0.785, $p < 0.001$), CK-MB (r: 0.480, $p < 0.05$) and CRP (r: 0.609, $p < 0.05$).

The control group was in normal histological appearance in the examination of Masson's trichrome stain applied under light microscope to show the formation of connective tissue in cardiac tissues (Fig. 1a). In the 6th hour group, the number of inflammatory cells increased (black arrows) (Fig. 1b) and in the 24th hour group the number of inflammatory cells increased (black arrows) as well as congestion (red arrows), edema and deterioration of tissue integrity (black star) (Fig. 1c). In the 7th day group, a significant increase was observed in

Table 1
Levels of all measured parameters.

Parameters	Group I (Control) (Mean ± SD) (n:6)	MI Groups (Mean ± SD)			*p* value
		Group II (6 h) (n:6)	Group III (24 h) (n:6)	Group IV (7th day) (n:6)	
Visfatin (ng/mL)	20.7 ± 4.3	208.5 ± 101.8[a]	243.1 ± 120.2[b]	24.1 ± 12.6[c]	a: 0.040 b: 0.020 c: 0.937
Troponin T (ng/mL)	0.020 ± 0.004	2.282 ± 0.356[a]	0.994 ± 0.0459[b]	0.030 ± 0.012[c]	a: 0.020 b: 0.030 c: 0.485
AST (U/L)	190.2 ± 10.5	252.3 ± 36.5[a]	242.5 ± 47.8[b]	210.8 ± 55.5[c]	a: 0.010 b: 0.010 c: 0.485
CK- MB (U/L)	687.7 ± 40.6	978.7 ± 308.3[a]	814.3 ± 252.0[b]	679.5 ± 203.2[c]	a: 0.090 b: 0.394 c: 0.494
CRP (mg/L)	1.16 ± 0.14	1.37 ± 0.35[a]	1.94 ± 0.96[b]	1.15 ± 0.22[c]	a: 0.026 b: 0.020 c: 0.699
LDH (U/L)	1075 ± 130.6	1393 ± 307.3[a]	1351 ± 396.3[b]	1195 ± 196.5[c]	a: 0.065 b: 0.240 c: 0.554

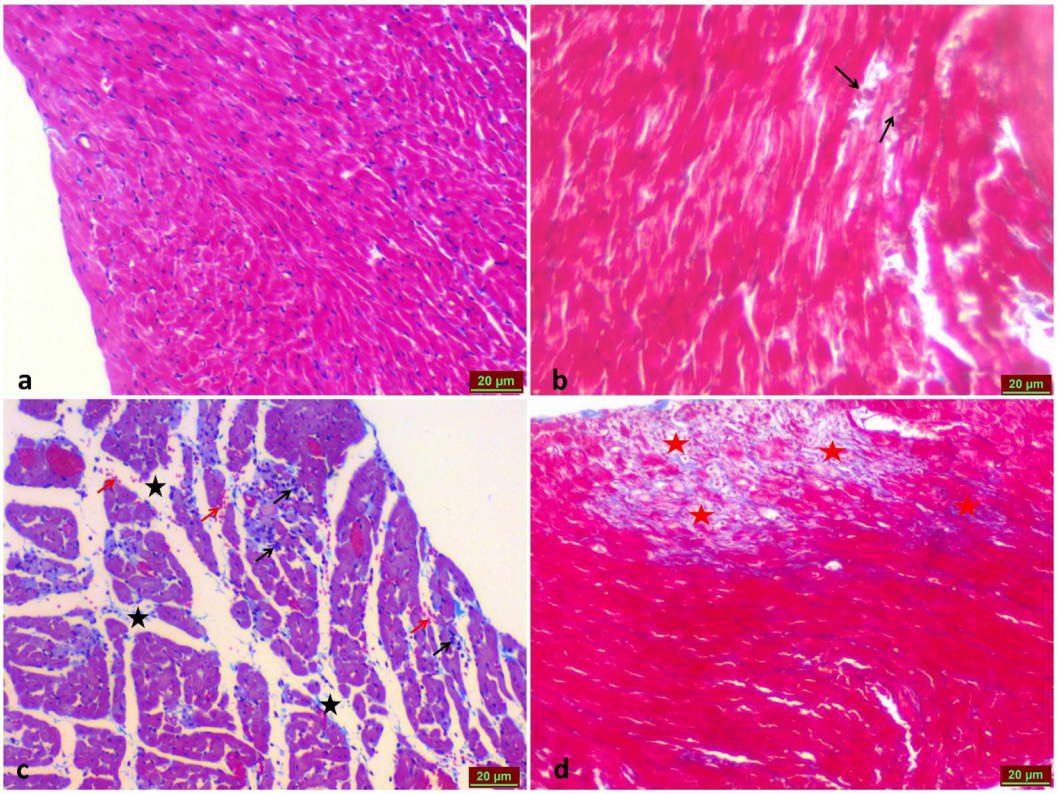

Fig. 1. Histological injury of cardiac tissues (Masson's trichrome staining) for the whole time period (control (a), 6 h (b), 24 h (c), and 7 day (d)) of observation.

the connective tissue (red[1] star) (Fig. 1d).

Visfatin immunoreactivity was observed in normal cardiac cells (black arrow) in the immunohistochemical examination of the control group (Fig. 2a). When compared with the control group, it was observed that the visfatin immunoreactivities increased statistically significantly ($p < 0.05$) in 6th hour (Fig. 2b) and more significantly in the 24th hour group (Fig. 2c). The visfatin immunoreactivity in the 7th day group was similar to the control group. When compared to the 6th hour group, visfatin immunoreactivity increased statistically significantly in the 24th hour group (Fig. 2d) ($p < 0.05$) (see Table 2)

4. Discussion

Serum visfatin levels increased during the 6th and 24th hours in our study. These results were consistent with previous studies [16,18]. After MI, lymphocytes and macrophages transcend the vessel wall and play a major role in inflammation [19]. On the fifth day after MI, macrophages reach the necrotic zone and show their highest activity approximately in the third week [20]. The rapid increase of neutrophils and monocytes in MI can also account for the high levels of visfatin in

[1] For interpretation of color in Fig. 1, the reader is referred to the web version of this article.

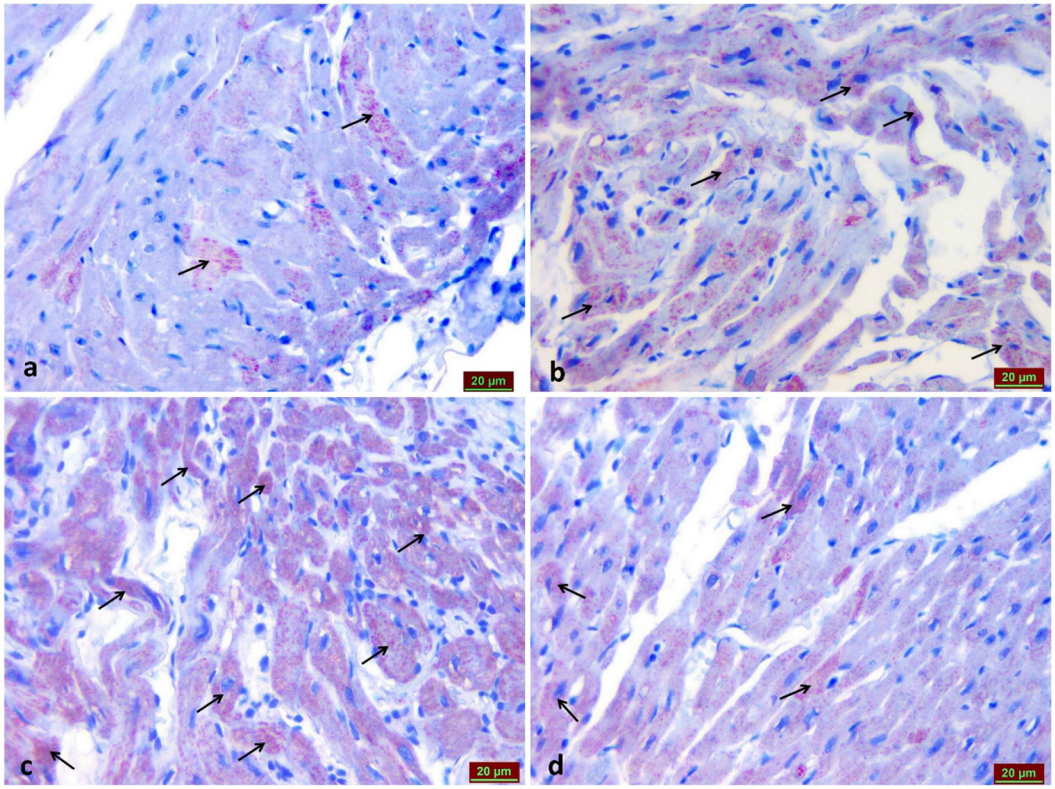

Fig. 2. Visfatin immunoreactivity (control (a), 6 h (b), 24 h (c), and 7 day (d)).

Table 2
Visfatin immunoreactivity.

Groups		Histoscores (Mean ± SD)	*p* value
Group I (Control) (n:6)		0.36 ± 0.10	
MI Groups	Group II (6 h) (n:6)	0.83 ± 0.19	0.003
	Group III (24 h) (n:6)	2.55 ± 0.36	0.001
	Group IV (7thday) (n:6)	0.25 ± 0.12	0.452

our study. It is also known that visfatin levels increase through hypoxia-induced Factor-1 alpha [21]. Therefore, ischemia after MI can be shown as one of the causes of visfatin increase.

Increased cardiac fibroblasts and excessive accumulation of the extracellular matrix are the basis of myocardial fibrosis. In their articles published by Yu et al. [22] in 2010, visfatin has shown to increase dose and time-dependent cardiac fibrosis. Visfatin plays a role in cardiac fibrosis by proliferating on fibroblasts and increasing type I and III collagen release [22]. In the immunohistochemical studies we performed, visfatin increase in cardiac tissue at 6th and 24th hours after MI suggests that visfatin plays an active role in reorganization and healing process. In our study, it was observed that visfatin levels decreased in circulation and cardiac muscles at 7th day after MI. This decrease may be attributed to decreased inflammatory cells and fibroblasts after the onset of fibrosis. It may also be due to the avoidance of excessive fibrosis during cardiac healing in the post MI period.

The troponin T test was used to demonstrate the occurrence of MI in our study and its levels peaked at 6th and 24th hours and decreased to control levels at 7th day. We also observed that serum visfatin levels peaked at 6th and 24th hours and decreased at 7th day so it was similar to troponins' changes. Immunohistochemically, cardiac visfatin changes were similar to those in serum, suggesting that circulating visfatin may be cardiac-derived.

Fukuhara and colleagues [9] observed that glucose levels were reduced within 30 min after administration of recombinant visfatin, but glucose levels returned to control levels after 60 min. This effect of rapid formation and termination of visfatin probably occurs during ischemia. This feature may suggest that changes in visfatin levels in the early stages of cardiac damage may be used as changes in other cardiac markers. In our study, the association of visfatin levels with troponin T was found to support this observation. High immunomodulation of visfatin activity in the cardiac tissue during immunohistochemical staining supports the cardiac specificity of visfatin.

Mazaherioun et al. [23] found increased visfatin levels in the study of 72 patients and 83 healthy subjects who applied at 8 h after MI. In addition, the study of Lu et al. [24] examined the change of visfatin levels in STEMI patients until the end of the first month after angiography and visfatin levels have been shown to be proportional to cardiac markers. They observed that visfatin levels increased rapidly until the 24th hour and fell to control levels at the end of the first week and did not change for a month. In the same study, it was observed that when the left ventricular immunohistochemistry was examined in the rat experiment in which coronary artery ligation was established, the amount of visfatin increased. It is minimally affected by both environment and individual-based changes, since our study is an experimental MI model. In our study, the changes in visfatin levels from the first hours to the 7th day are parallel to the findings of Lu and his colleagues. In addition, histological findings supported each other. The correlation between troponin T and visfatin in our study was also in agreement with the correlations between Lu and colleagues troponin I and visfatin.

One of the largest analyzes that examined the relationship between Visfatin and MI was performed by Yang et al. In 2014 [15]. They reviewed MI and visfatin-related 56 publications published before May 2013 and they selected to analyze 11 case-control studies published between 2009 and 2012. As a result, 362 MI and 322 healthy individuals were included in the meta-analysis and visfatin levels were found to be elevated in the MI group when compared to healthy

subjects. They emphasized that elevated visfatin levels are associated with the risk of MI formation and that visfatin may enter into reliable cardiac markers in the future. So this comprehensive analysis and our results were consistent.

In our study, classical MI markers AST and LDH levels were also measured but the results were not satisfactory due to intense hemolysis. Because the levels of visfatin and troponin were assessed by immunological methods, hemolysis was less effective. It may be more beneficial to take an intracardiac sample so that more appropriate results can be obtained.

4.1. Conclusion

Our study gives limited information as the number of subjects. It also includes acute and subacute episodes after experienced MI. Longer-term observations will be more appropriate to demonstrate the effects of visfatin in the chronic phase. However, our study shows the time-dependent changes of visfatin levels for the first time in the experimental MI model. It is a distinct advantage of our study that includes MI formation and the following 7 days. Comparisons of cardiac markers and visfatin levels may provide guidance for a new cardiac marker. Visfatin, like troponins, increases both in heart and circulation, indicating that it may be a cardiac marker. We believe that visfatin may be an important marker for the diagnosis and prognosis of MI if supported by more extensive studies.

5. Conflict of interestxxx

The authors declare that they have no conflict of interest.

6. Authors' contributions

Mehmet Erten, İclal Geyikli Çimenci, Tuncay Kuloğlu, Mehmet Kalaycı and Füsun Erten contributed to the conduct of the research, data collection and analysis. All authors gave final approval of the version to be published.

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