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Original Article

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Cardiometabolic Role of Visfatin in Patients on Peritoneal Dialysis

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Abstract

Objective: There is a relationship between inflammation and cardiovascular disease (CVD) in patients with chronic kidney disease. Visfatin is an adipocytokine, which has been shown to be associated with inflammation, endothelial dysfunction, and CVD. Our study aimed to examine the relationship of visfatin with metabolic and echocardiographic parameters in patients on peritoneal dialysis (PD).

Materials and Methods: A total of 50 patients (mean age, 51.9±15.3 years; 29 women) followed up in our unit, and 31 healthy controls were enrolled in our study. Demographic characteristics, routine laboratory tests, echocardiographic findings, flow-mediated dilatation (FMD) percentages, and visfatin levels of the individuals were recorded.

Results: No significant difference was found in the mean serum visfatin level of patients on PD compared with that of the control group (11.95±4.37 ng/mL and 13.43±6.68 ng/mL, respectively; p=0.384). Visfatin was positively correlated with serum glucose level (r=0.298, p=0.036), levels of uric acid (r=0.404, p=0.004), sodium (r=0.313, p=0.027), alanine aminotransferase (r=0.344, p=0.015) and negatively correlated with left ventricle end-diastolic diameter (LVEDD) (r=-0.305, p=0.031) in univariate analyses. Other echocardiographic parameters and FMD showed no correlation with visfatin. Significant association was found between visfatin and LVEDD (cm) (B=-0.087, beta=-0.334, p=0.011), uric acid (mg/dL) (B=0.042, beta=0.287, p=0.033), and sodium (mmol/L) (B=0.012, beta=0.277, p=0.038) in linear regression analysis.

Conclusion: Visfatin is an adipocytokine with a potential relationship with cardiac remodeling, metabolic diseases, and water-salt balance in patients on PD.

Keywords: Cardiovascular disease, chronic kidney disease, inflammation, peritoneal dialysis, visfatin

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INTRODUCTION

Cardiovascular diseases (CVDs) are responsible for more than half of the mortalities in patients with end-stage renal disease (ESRD), and risk of mortality increases 20-30 times in these patients compared with the general population (1). Left ventricle hypertrophy (LVH), which has been shown in approximately 70% of the patients on dialysis, and systolic dysfunction are associated with high cardiovascular mortality in these patients (2). LVH is more severe in patients on peritoneal dialysis (PD) than patients on hemodialysis (HD), and this is attributed to insufficient fluid control (3). Some nontraditional factors, such as inflammation, oxidative stress, endothelial dysfunction, sympathetic activation, and protein carbonylation, have been suggested as the risk factors for the development of CVD in patients with chronic kidney disease (CKD) (4).

Visfatin (nicotinamide phosphoribosyltransferase or NAMPT) is a polypeptide including 491 amino acids, and its gene is found in the long arm of the 7th chromosome (5). Visfatin is a proangiogenic molecule. It has been determined to reduce the level of matrix metalloproteinase tissue inhibitors and increase the expression and ac-

tivation of matrix metalloproteinase-2 and 9, the enzymes that facilitate extracellular matrix degeneration and angiogenesis. Vascular endothelial cell growth factor is responsible for some of the proliferative effects of visfatin in the endothelial cells (6). It was shown that visfatin levels were higher in patients with type-2 diabetes than the control group and particularly higher in patients with severe proteinuria than in patients with mild proteinuria (7).

In contrast, there are studies suggesting that visfatin might have a role in CVD, diabetes mellitus (DM) and obesity-related conditions, endothelial functions, and ischemic cerebrovascular diseases (7-11). In our study, we aimed to investigate the relationship of visfatin with cardiac functions and other metabolic parameters in patients on PD.

MATERIALS AND METHODS

A total of 69 patients followed up in the PD unit of our hospital between 2010 and 2011, who agreed to participate in the study, were included in our cross-sectional study. Patients under 18 and over 80 years, those who had PD for less than 3 months, and those with cardiac valve disease and dysrhythmias like atrial fibrillation, active systemic infections or peritonitis within the past month, malignant disease, and clinically significant hypervolemia or New York Heart Association class 3 and 4 cardiac failure were excluded from the study. A total of 50 patients on PD were included in the study. A control group of 31 healthy individuals with no known cardiac or renal disease were included for comparison of the serum visfatin levels. Demographic data of the patients (age, sex, weight, height, and body surface area along with their primary renal diseases, CKD and PD duration, and PD treatment modalities and medications), Kt/V measurements, and dialysate/plasma creatinine ratio at the 4th hour in peritoneal equilibration test (D/P creatinine) were recorded. Urine amount higher than 200 mL/day was accepted as significant residual renal function (RRF). Blood samples were taken after 12 hours of fasting for routine hematologic and biochemical tests, and analyses were carried out in accordance with routine laboratory methods manufacturer directions using Siemens Advia 2400 autoanalyzer and ABX Pentra DX120 device. Visfatin measurement was studied with Phoenix Pharmaceuticals (Belmont; CA USA) branded human visfatin kit. Echocardiography was performed to assess the cardiac structure and function, and brachial artery flow-mediated dilatation (FMD) tests were also performed to assess the endothelial functions in all patients.

Main Points

- Positive correlations were found between visfatin and glucose, uric acid, ALT and sodium levels.
- A negative correlation was found between visfatin and LVEDD.
- Visfatin might have potential relationship with cardiac remodeling, metabolic diseases and water-salt balance in patients on PD.

Echocardiography

Echocardiographic exams of the patients were carried out by the same physician with a General Electric Vivid-7 echocardiography device. Cardiac space measurements and ventricle diameters were calculated by M-mode measurement. Ejection fraction (EF) was computed using Modified Simpson method. Left ventricle weight was calculated using the Devereux Formula, the resulting value was divided by the patient's body surface area, and the left ventricle mass index (LVMI) was found. LVH was accepted as >110 g/m^2 for women and >134 g/m^2 for men (12).

Assessment of Endothelial Function

The FMD was performed with ultrasound measurement technique of brachial artery using Vingmed System Five, Horten, Norway device connected to 10 MHz linear transducer. The patients were advised not to consume any alcoholic drinks or caffeine and to avoid exercise in the last 12 hours, and the FMD test was performed after 8-12 hours of fasting. The test was performed at 21°C-23°C. Blood pressures were measured after 10 minutes of resting. Brachial artery diameter of the dominant arm was measured in 3 cardiac cycles with the patients in the supine position, and the averages were recorded as basal value. The sphygmomanometer cuff was held for 5 minutes at over 200 mm Hg to obtain ischemia in the forearm. The cuff was then deflated, and the inner diameter measurement of the brachial artery was repeated after 60 seconds. FMD was stated as the increase compared with the basal level. The formula used for FMD measurement was (arterial diameter after deflation of cuff-basal artery diameter/basal artery diameter) ×100 (13).

Statistical Analysis

The data obtained were transferred to the Statistical Package for the Social Sciences (SPSS) file prepared exclusively for the study. Further assessment and statistical examination were carried out using SPSS 15.0 for Windows standard version (SPSS Inc.; Chicago, IL, USA). Numerical data were provided as mean±standard deviation. Student t test or Mann-Whitney U test, when needed, was used to compare the 2 groups. For nonnumerical data, the Yates corrected chi-squared test and Fisher's exact test were used for 2×2 probability tables, when appropriate. Analysis of correlations between the numerical parameters was performed using Pearson's correlation, and correlations between the nonnumerical parameters were determined using the Spearman's Rho correlation test; $p<0.05$ was accepted as significant. Parameters related to plasma visfatin level in univariate analyses were analyzed with linear regression analysis with the "enter" method for multivariate analysis.

RESULTS

A total of 50 patients on PD treated in our PD unit were enrolled in this study, and 29 (58%) of the patients were women and 21 (42%) were men; 31 patients (62%) were on continuous ambulatory PD (CAPD), and 19 (38%) patients were on automated PD. A total of 30 (60%) patients had significant RRF. DM was the most

common cause in ESRD etiology (13; 26% of the patients), and 38 (76%) of the 50 patients had hypertension (HT) as a comorbidity. The mean blood pressure was 129±22/80±11 mm Hg. The demographic data, primary renal diseases, and comorbidities of the patients are summarized in Table 1. There were 17 women (55%) and 14 men (45%) in the healthy control group. The mean age of the control group was 41.3±10.7 years, which was significantly lower than that of the patients (p<0.001). Sex distribution of the control group (54.8%; 17 women) was not different from the patient group (56.6%; 30 women) (p=0.87). There was no significant difference between the patient and control groups in terms of body-mass index (BMI) (27.7±6.5 kg/m^2 and 25.8±6.2 kg/m^2, respectively; p=0.19). The laboratory and echocardiography findings of the patients in our study are summarized in Tables 2 and 3. There was no significant difference in the visfatin levels between the patient and the healthy control groups (11.95±4.39 ng/mL and 13.4±6.69 ng/mL, respectively; p=0.384). The mean visfatin levels did not differ between men and women in the patient group (12.46±3.68 and 11.58±4.86, respectively; p=0.227) and in the control group (11.51±5.26 and 15.03±7.45, respectively; p=0.297). Visfatin level was not significantly different in the patients with and without ischemic heart

Table 1. Demographic data of patients, primary diseases causing end-stage kidney disease, and distribution of comorbidities

Characteristics		Patient group (n=50)
Age (year)		51.9±15.3
Sex (female/male)		29/21
BSA (kg/m^2)		1.74±0.20
BMI (m^2)		27.8±6.5
Duration of CKD (year)		7.5±4.7
Duration of PD (month)		42.8±24.9
Primary kidney diseases n (%)	Hypertensive nephrosclerosis	7 (14)
	Unknown	13 (26)
	Diabetic nephropathy	13 (26)
	Glomerulonephritis	6 (12)
	ADPKD	3 (6)
	Postrenal causes	8 (16)
Comorbidities n (%)	HT	38 (76)
	DM	14 (28)
	Hyperlipidemia	21 (42)
	Ischemic heart disease	7 (14)

BSA: body surface area; BMI: body-mass index; CKD: chronic kidney disease; PD: peritoneal dialysis; ADPKD: autosomal dominant polycystic kidney disease; HT: hypertension; DM: diabetes mellitus

Table 2. Biochemical parameters of the patients

Parameters	Mean±SD	Minimum	Maximum
Glucose (mg/dL)	137.5±83.7	72.0	479.0
Urea (mg/dL)	102.7±33.7	11.2	211.0
Creatinine (mg/dL)	8.2±2.8	4.2	16.3
Uric acid (mg/dL)	5.9±1.0	4.0	8.8
Sodium (mmol/L)	138.2±3.8	130.0	148.0
Potassium (mmol/L)	4.1±0.7	3.0	6.0
Calcium (mg/dL)	9.1±0.6	7.9	10.3
Phosphorus (mg/dL)	5.1±1.2	2.9	8.6
Calcium×phosphorus (mg^2/dL^2)	46.7±12.2	24.0	77.0
Parathormone (pg/mL)	574±436	80	1,900
Total protein (g/dL)	6.5±0.8	5.0	8.5
Albumin (g/dL)	3.8±0.4	2.7	4.5
Total cholesterol (mg/dL)	189±45	113	338
HDL-cholesterol (mg/dL)	42±17	20	90
LDL-cholesterol (mg/dL)	113±35	58	235
Triglyceride (mg/dL)	171±92	35	475
AST (U/L)	16±6	6	37
ALT (U/L)	17±8	5	39
ALP (U/L)	134±199	45	1,428
Hemoglobin (g/dL)	10.8±1.3	7.5	14.3
Ferritin (ng/mL)	382±328	24	1,650
CRP (mg/dL)	1.9±4.3	0.1	26
Visfatin (ng/mL)	11.95±4.39	5.1	29.5
Total Kt/V	2.5±0.67	1.42	4.0
D/P creatinine ratio (4th hour)	0.67±0.09	0.47	0.87

SD: standard deviation; HDL: high-density lipoprotein; LDL: low-density lipoprotein; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase; CRP: C-reactive protein; D/P: dialysate/plasma

disease (IHD), HT, hyperlipidemia, and RRF. These findings are summarized in Table 4.

In correlation analyses of the PD group, a positive correlation was found between visfatin and glucose, uric acid, sodium, alanine aminotransferase (ALT) (r=0.298, p=0.036; r=0.404, p=0.004; r=0.313, p=0.027; r=0.344, p=0.015, respectively). No relationship was found between visfatin and hemoglobin, ferritin, and C-reactive protein in correlation analyses. Furthermore, no correlation was present between visfatin and D/P creatinine level. In the echocardiographic parameters, a negative correlation was found between visfatin and left ventricle end-diastolic diameter (LVEDD) (r=-0.305, p=0.031). Other echocardiographic parameters showed no correlation with visfatin. There was no correlation between visfatin and FMD (r=0.033, p=0.838). In the linear regression analyses, LVEDD (cm) (B=-0.087, beta=-0.334, p=0.011), uric acid (mg/dL) (B=0.042, beta=0.287, p=0.033), and sodium (mmol/L) (B=0.012, beta=0.277, p=0.038) were shown to have a significant relationship with the serum visfatin levels (Figure 1).

Table 3. Echocardiographic findings of patients

Characteristics	Mean±SD	Minimum	Maximum
Left atrium diameter (cm)	3.56±0.56	2.10	4.90
Left ventricle end-diastolic diameter (cm)	4.61±0.58	3.30	5.70
Left ventricle end-systolic diameter (cm)	2.98±0.58	2.10	4.80
Left ventricle posterior wall thickness (cm)	1.14±0.17	0.80	1.60
Ejection fraction (%)	62.94±7.9	32.0	75.0
Interventricular septum wall thickness (cm)	1.25±0.22	0.90	2.00
Right ventricle diameter (cm)	2.54±0.26	2.00	3.40
Aortic diameter (cm)	3.20±0.32	2.40	3.90
Pulmonary artery diameter (cm)	2.09±0.25	1.70	3.00
Left ventricle mass (g)	248.4±84.2	86.9	470.2
Left ventricle mass index (g/m^2)	141.6±42.9	58.0	270.0

SD: standard deviation

DISCUSSION

Our study revealed a positive correlation between visfatin and glucose, uric acid, ALT, and sodium levels and a negative correlation with LVEDD. This relationship continued between visfatin and LVEDD, uric acid, and sodium in multivariate analyses. This suggests that LVEDD is a weaker indicator than other known parameters (EF, LVMI, and so on) in determining the cardiac structure and function, and there are human and animal studies that support these data. It was seen that visfatin affected proliferation and collagen synthesis in rat cardiac fibroblasts, and it was suggested to have a likely role in myocardial

Table 4. Comparison of visfatin levels between patients with and without HL, HT, IHD, and RRF

		Visfatin	
		Mean	SD
HL	(+)	11.42	4.06
	(-)	12.28	4.49
HT	(+)	11.91	4.51
	(-)	12.01	3.70
IHD	(+)	11.71	3.00
	(-)	11.98	4.55
RRF	(+)	12.02	4.54
	(-)	11.8	4.04

SD: standard deviation; HL: hyperlipidemia; HT: hypertension; IHD: ischemic heart disease; RRF: residual renal function

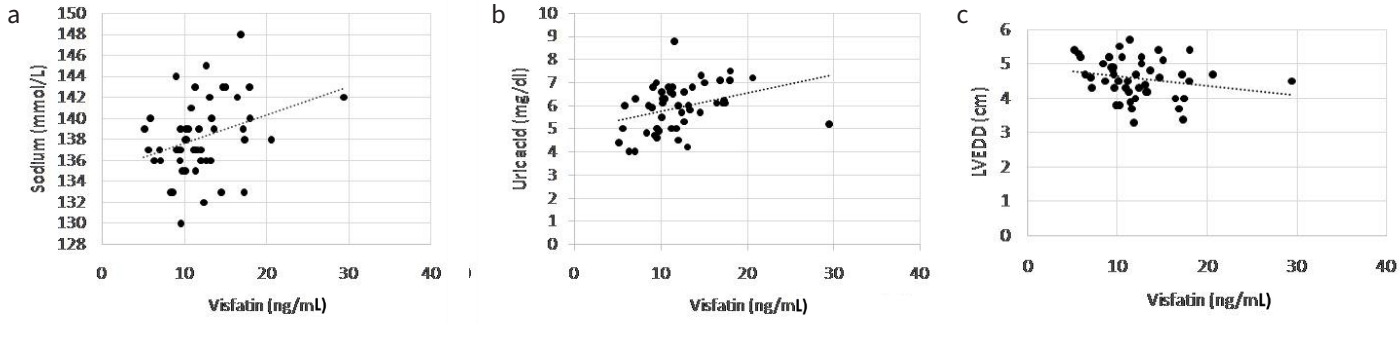

Figure 1. a-c. Correlation graphics of visfatin with a) sodium, b) uric acid, and c) left ventricle end-diastolic diameter

fibrosis (8). Multiple cardiac studies involving different patient groups demonstrate the importance of LVEDD in the direct measurement of cardiac functions (EF is an essential criterion in the measurement of prognosis, including diastolic LV filling) as well as prognostic significance by demonstrating LVEDD with cardiac computed tomography. There are many studies that suggest the prognostic importance of this subject (14-17).

There are also important studies on these topics in patients on PD. For example, in a study by Hüting et al. (18) in patients with CAPD, they showed that diastolic filling is impaired by observing LV systolic and diastolic filling, which is independent of LV hypertrophy. A study by Facchin et al. (19) examining the detailed echocardiographic parameters in patients with CAPD showed that deterioration in LVEDD (independent of blood pressure, LV hypertrophy, and metabolic parameters) besides some parameters related to left ventricular diastolic function indicated impairment in myocardial relaxation, specifically called uremic cardiomyopathy.

Moreover, in their study with NAMPT transgenic mice, Pillai et al. (9) found out that visfatin increased cardiac fibrosis and caused negative ventricular remodeling. A literature review for studies on visfatin and patients on PD unearthed a study by Karakan et al. (10), which showed a correlation between visfatin and LVMI. A study by Erten et al. (20) determined that visfatin had a negative effect on the left ventricular functions and no relation to LVMI. Considering the previous experimental and clinical studies and our study, we interpreted that visfatin might be associated with cardiac diseases and remodeling.

It has been known for many years that uric acid is associated with HT and CVD (21). In our study, visfatin levels did not present any significant difference between patients with and without IHD and HT. It was reported that visfatin had a role in the deterioration of endothelial function in patients with CKD; therefore, visfatin could cause atherosclerosis. It has been shown that increased visfatin levels correlate positively with high-sensitivity C-reactive protein and artery occlusion and may be responsible for myocardial infarction (22, 23). Hence, we researched the relationship between visfatin levels and markers, such as uric acid, related to atherosclerosis. Visfatin showed a significant correlation to serum uric acid levels, both in the univariate (r=0.404, p=0.004) and multivariate (B=0.042, beta=0.287, p=0.033) analyses. A significant relationship was present in the study of Lu et al. (11) between visfatin and serum uric acid levels in patients with CKD, both in the univariate and multivariate analyses, similar to our study. A correlation was observed between the visfatin and serum uric acid levels in the study carried by Karakan et al. (10) in univariate analyses; however, this relationship was not found in the stepwise regression analysis. It is stated that visfatin has an insulin mimetic impact on cultured cells. Visfatin binds and activates the insulin receptors, which results in low plasma glucose levels in animal models (24). Visfatin is an adipocytokine released from the visceral adipose tissue and is known to have an insulin-like effect (25). Considering the association between visfatin and glucose in our study with all of these findings, this association between visfatin and uric acid supports the view that visfatin plays a role in the pathogenesis of the metabolic syndrome, which is quite common in patients on PD (26).

We found a significant correlation between visfatin and sodium levels in our study. The literature review did not reveal any study on this aspect in CKD and patients on dialysis or other patient populations. We have interpreted our result to be probably related to the association between visfatin and the body's fluid and salt balance. More detailed studies are needed about this aspect.

In our study, visfatin levels were not different between the patient and control groups. In some studies, including patients on PD and HD (27), as in our study, it was reported that visfatin levels were not different between the patients and individuals in the uremic groups. Our study supports this data. In contrast, there are articles stating that visfatin level is higher among patients on PD, and this may be related to the glucose load in PD (20). The main reason for these differences could be that there was no significant difference in BMI between the patient and control groups, as in our study. However, in another study conducted with patients on HD (28), although there was no difference in BMI between the HD and the control groups, visfatin level was found to be significantly higher in the HD group.

However, in this study, a significant difference was detected in the adipose tissue measurement (fat mass%) between the patient and control groups (24.5±8.6 and 29.1±9.8, respectively; p=0.017). This suggests that the main relationship between BMI and visfatin level is related to body fat ratio.

It is already known that visfatin is an adipocytokine, circulating visfatin levels increase in obese individuals, and it positively correlates with BMI (29). However, there are no data directly linking visfatin levels to the grade of renal failure.

Although some studies revealed a significant relationship between visfatin levels and FMD, an indicator of endothelial function, we did not find any such relationship. These different results might be owing to the difference in the patient numbers and the population enrolled in the study. A study on patients with type-2 DM showed a negative correlation between visfatin levels and FMD percentage (8, 9). The reason for the lack of correlation in our study might be explained by the multiple uremic factors affecting endothelial functions in ESRD and the factors specific to PD.

We could not show a relation between visfatin and peritoneal equilibration test parameters (peritoneal clearances and permeability). In concordance, two different studies also did not demonstrate a relationship (10, 27). Visfatin levels did not show

a significant difference between the applied PD treatment modalities or between the patients with and without RRF either.

In our study, no significant relationship was found between body surface area and visfatin levels, both in the patient and healthy control groups. We also could not establish any significant relationship between visfatin levels of patients on PD with and without DM. No correlation was found between the hemoglobin (Hb) A1c levels. Visfatin is defined as an antidiabetic adipocytokine, and its effects on the beta cells are not clearly understood. Visfatin level was found to be higher in patients with newly diagnosed type-2 DM than that of the control group in a study conducted by Dogru et al (30). The fact that we did not observe any relationship between diabetes and HbA1c was probably because of the difference in the patient groups because there is a possibility that high glucose content of PD solutions and uremic toxins might interact with insulin secretion and visfatin levels.

CONCLUSION

Visfatin might be an adipocytokine with a potential relationship with cardiac remodeling, metabolic diseases, and water–salt balance in patients on PD. Further extensive research on this is warranted.

Ethics Committee Approval: Ethics committee approval was not received for this study.

Informed Consent: Informed consent was not obtained due to the nature of this study.

Peer-review: Externally peer-reviewed.

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