ORIGINAL ARTICLE

Eastern Journal of Medicine
East J Med 25(2): 218-224, 2020
DOI: 10.5505/ejm.2020.27122

The Association of Visfatin Levels With Metabolic Parameters and Inflammation In Diabetic Nephropathy

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ABSTRACT

To investigate the visfatin levels at the stages of diabetic nephropathy(DNP), changes in visfatin levels according to stages of DNP, and the association of visfatin levels with other anti-inflammatory parameters including high sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6), and tumor necrosis factor alpha(TNFα).

Patients were divided into 4 groups based on the glomerular filtration rate (GFR) and albuminuria as follows; *Group I:* albuminuria<30 mg per day and GFR>60ml/min, *Group II:*albuminuria 30 to 300 mg per day and GFR>60ml/min, *Group III:*albuminuria>300mg per day and GFR>60ml/min, and *Group IV:*albuminuria>300 mg per day and GFR<60 ml/min.

Of the 141 patients included in the study, 83(58.8%) were female. The mean age of patients was 55.3±8.2 years. Microalbuminuria was found to be 10.1±9.8 mg per day in group I, 89.4±68.2 mg per day in group II, 525.1±280.7 mg per day in group III, and 1034±1893 mg per day in group IV ($p<0.001$). When the correlation analysis was repeated separately in each group, there was a positive correlation between Visfatin and IL-6 levels in only group III ($r=0.926$; $p<0.001$). When the patients in group III and IV were combined in a single group and considered as macro-albuminuric, multivariate analysis showed that visfatin had a positive correlation with IL-6 ($r=0.380$, $p=0.006$)

In this study, we could not determine any association between visfatin levels and other anti-inflammatory markers (IL-6, TNFα, and hsCRP). However, we found a close relationship between visfatin levels and IL-6 which is one of the most important markers of inflammation in diabetic patients with overt nephropathy, namely macro-albuminuric patients.

Key Words: Diabetes mellitus, diabetic nephropathy, visfatin, inflammation marker

Introduction

Diabetes mellitus (DM) is a metabolic disease in which the organism cannot sufficiently utilize carbohydrates, fats, and proteins due to the lack of insulin or insulin effect, requiring a continuous medical care and leading to acute metabolic complications as well as long-term vascular, renal, retinal, or neuropathic complications (1, 2).

Diabetic nephropathy (DNP) is a common microvascular complication of both Type I- and Type II-DM and one of the major reasons of morbidity and mortality. It is also an important cause of end-stage renal disease (ESRD). DNP develops in 30-35% of Type I- and Type II-diabetic patients. Recent studies show that pro-inflammatory factors and cytokines play important roles in the development of DNP (2, 3).

Adipokines are a group of highly expressed proteins or cytokines derived from adipocytes, with a distinct of biological functions including energy balance, lipid metabolism, glucose balance, and inflammation. In some cases where adipose tissue mass is increased, the amount of these proteins (adipokines) also increases. Among these proteins, resistin, interleukin-6 (IL-6), and tumor necrosis factor alpha (TNFα) play important roles in the emergence of insulin resistance in obesity. Moreover, adipokines such as adiponectin and leptin stimulate beta oxidation of fatty acids in skeletal muscle, resulting in less insulin use. In addition, chemerin, vaspin, apelin, omentin, and visfatin are also an adiponectin (4-7).

Visfatin is an adipocytokine involved in obesity and obesity-related metabolic diseases. While many studies have reported that visfatin levels increase in obesity, diabetes, and cardiovascular disease, some studies have shown opposite results. Visfatin has also been shown to increase the leukocyte activation, adhesion molecule synthesis, and pro-inflammatory cytokine production (8, 9).

Novel anti-inflammatory treatment methods are needed for early detection and prevention of DNP

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Received: 06.02.2020, **Accepted:** 14.03.2020

development (9). Herein we aimed to analyze the visfatin levels at different stages of DNP, changes in visfatin levels by stages of DNP, and the relationship of visfatin with other anti-inflammatory parameters such as IL-6, TNFα and high sensitivity C-reactive protein (hsCRP).

Material and Methods

Data Collection: This was a study of patients with DNP who were followed up in a nephrology outpatient clinic. The diagnosis of DM was made pursuant to the ADA criteria as follows; *fasting blood glucose (FBG) level ≥ 126 mg/dl, *plasma glucose level at any hour of the day in the event of clinical symptoms without starvation > 200 mg/dl, *two-hour plasma glucose level during oral glucose tolerance test> 200 mg/dl, or *HbA_{1c} ≥ 6.5%.

Patients with the following criteria were excluded from the study; age <18 or >70 years, type I-DM, transient urinary abnormalities, non-diabetic renal disease, chronic liver disease, positive serology for hepatitis or transaminase values >at least twice the upper limit of normal, autoimmune or malignant disease, advanced heart or lung disease, and systemic infectious disease, ischemic vascular disease in the last 3 months or inflammatory disease.

Age, gender, presence of renal failure, duration of DM, and the time period since diagnosis of renal failure were recorded. Among the physical examination findings, height, hip circumference, weight, and waist circumference were recorded. For body mass index (BMI) formula as follows; BMI = Weight (kg)/ height^2 (m). After 12 hours of fasting, venous blood samples were taken from all patients and placed into dry tubes without gel and EDTA tubes. The blood samples were then centrifuged at 1000 x g for ten minutes. Samples were stored at -80 ºC. Biochemical examinations were performed by dissolving serum and plasma at the time of analysis. Based on the glomerular filtration rate (GFR), microalbuminuria, and proteinuria measured at least in two separate days in the last 3 months, patients were splited into 4 groups as follows; *Group I:* Patients with albuminuria less than 30 mg per day and GFR greater than 60 ml/min, *Group II:* Patients with albuminuria = 30 to 300 mg per day and GFR greater than 60 ml/min, *Group III:* Patients with albuminuria >300 mg per day and GFR higher than 60 ml/min, and *Group IV:* Patients with albuminuria > 300 mg per day and GFR less than 60 ml/min.

Laboratory Data: The following biochemical parameters were measured in all patients; glucose, hemoglobin A_{1c} (HbA_{1c}), creatinine, urea,uric acid, potassium (K), sodium (Na), calcium (Ca), total protein, phosphorus (P), albumin, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglyceride, VLDL-cholesterol, aspartate transaminase (AST), hsCRP, alanine transaminase (ALT) IL-6, TNFα, and visfatin. Insulin resistance (HOMA-IR) was calculated as follows; HOMA-IR: FBG (mg/dl) x Fasting insulin (micruU/ml)/405. Biochemical parameters including glucose, creatinine, urea, uric acid, K, Na, Ca, total protein, P, albumin, total cholesterol, PTH, HDL, VLDL, LDL, triglyceride, ALT, AST, and ferritin levels were measured by Architect c1600 device according to the manufacturer's instructions. HbA_{1c} levels were measured by high-pressure liquid chromatography (HPLC) method using TOSOH C7 analyzer. Human TNFα and IL-6 levels were measured by ELISA method using BIOTEK EL 50 and BIOTEK EL 800 devices. Hematocrit (Hct), hemoglobin (Hb), total leukocyte count, platelet count, mean corpuscular volume (MCV), and ferritin levels were measured and then recorded. HORIBA Medical's ABX Pentra DX 120 hematology analyzer was used for the measurement of hematological parameters. GFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration formula. Microalbuminuria and proteinuria were calculated by according to the corresponding values in the spot urine by creatinine value in the spot urine.

Visfatin: Serum visfatin (antibody-coated 96-well plate human visfatin) was measured by BioVision's Enzyme-linked immunosorbent assay (ELISA) kit and absorbance was measured at 150 nm by an ELISA Bio-Tek (ELx800, Biomedical Technologies Inc. USA) microplate reader. The measurable range of visfatin is 0.0625 ng/mL - 16 ng/mL according to the manufacturer's information.

Statistical Analysis: Statistical package for the social sciences version 18.0 for windows was used for statistical analysis. Paired Student t-test or Mann Whitney U (if necessary) test was used for comparison of the two groups. For non-numerical data; chi-square test and Fisher's exact test were used in the analysis of 2x2 contingency tables. In the correlation analysis, Pearson test was used for normally distributed data and Spearman's rho correlation test was used for non-normally distributed data. Student t-test or, where necessary, one-way or multiple variance analysis (ANOVA) was used to compare the groups. Kruskal Wallis-H analysis was used to compare more than two groups in cases where data were not normally distributed. Tukey HSD was used for post-hoc comparison. Cox-regression analysis was performed to determine the factors affecting serum visfatin level. $p < 0.05$ was considered significant.

Ethics Committee Approval: This study was initiated after obtaining the ethics board approval from the Local Ethics Committee. Written informed consent was obtained from all patients eligible for the study.

Results

Of the 141 patients, 83 (58.8%) were female. The mean age of all patients was 55.3 ± 8.2 years. The age and gender distribution of the groups are summarized in Table 1. Duration of DM was 10.7 ± 7.9 years in the whole study group, 8.8 ± 7.1 years in Group I, 9.1 ± 6.9 years in Group II, 11.8 ± 9.3 years in Group III, and 13.5 ± 7.7 years in Group IV. There was a statistically significant difference between the groups in terms of DM duration ($p = 0.036$). The mean BMI of the patients was 29.2 ± 5.0 kg/m^2 in Group I, 32.2 ± 5.5 kg/m^2 in Group II, 30.2 ± 4.8 kg/m^2 in Group III, and 30.9 ± 4.9 in Group IV kg/m^2($p=0.085$) (Table 1).

Biochemical and hematological data of the groups and their comparisons among the groups are presented in Table 2. Hemoglobin, hematocrit, and ferritin levels were significantly lower in Group IV than those in Group I, II, and III. Serum urea, creatinine, phosphorus, and parathyroid hormone levels were significantly higher in Group IV than those in Group I, II, and III. While serum uric acid levels were significantly greater in Group IV than those in Group I and II, serum albumin level was lower. Insulin resistance was evaluated by HOMA-IR formula and the results were as follows; 4.4 ± 4.5 in group I, 4.9 ± 4.1 in group II, 7.0 ± 4.3 in group III, and 8.2 ± 5.5 in group IV ($p = 0.009$). Microalbuminuria was found to be 10.1 ± 9.8 mg/day in Group I, 89.4 ± 68.2 mg/day in Group II, 525.1 ± 280.7 mg/day in Group III, and 1034 ± 1893 mg/day in Group IV, with a statistically significant difference among the groups ($p < 0001$), except for Group I vs. Group II, and Group III vs. Group IV (Table 2).

The levels of hsCRP, Visfatin, IL-6, and TNFα in each group are presented in Table 5. The changes observed in these parameters at different stages of DNP are given schematically in Figure 2. A statistically significant difference was observed among the groups in terms of TNFα levels and this was due to the difference between Group II and Group IV ($p = 0.023$) (Table 3).

When the correlation analysis was repeated by evaluating the groups separately, there was a very positive correlation between Visfatin and IL-6 levels in Group III ($r=0.926$; $p<0.001$) and this was positively correlated with microalbuminuria ($r=0.560$; $p=0.01$) (Figure 1).

When the patients in group III and IV were combined in a single group as macro-albuminuric patients, univariate analysis showed that Visfatin was positively correlated with IL-6 ($r=0.386$, $p=0.003$), total protein ($r=0.332$, $p=0.006$), TNF-α ($r=0.257$, $p=0.036$), and age ($r=0.286$, $p=0.019$). However, in multivariate analyzes, the relation observed in univariate analysis was present only between visfatin and IL-6 (Table 4).

Discussion

In this study, we investigated the levels of visfatin and other anti-inflammatory markers (TNFα, IL-6, and hsCRP), changes in Visfatin levels, and the relation between Visfatin and other anti-inflammatory parameters at different stages of DNP. We could not detect a relationship between visfatin and other anti-inflammatory markers. However, visfatin was found to be closely associated with IL-6, which is an important marker of inflammation in diabetic patients with overt nephropathy, namely macro-albuminuric patients.

DNP, a common microvascular complication of both Type I- and Type II-DM, is one of the major causes of mortality and morbidity. It is also an important reason of ESRD. DNP develops in 30-35% of Type I- and Type II-diabetic patients [10-12].

Visfatin, which has been recently discovered and secreted predominantly from adipocytes, has been found to be identical to extracellular nicotinamide 5-phosphoribosyl-1-pyrophosphate transferase. Since nicotinamide is a rate-limiting step in adenine dinucleotide biosynthesis, it has crucial roles in energy metabolism, survival, and function of cells (106, 126). Visfatin has been accepted as a cytokine because it stimulates B-cell maturation and inhibits neutrophil apoptosis. Visfatin has also been shown to increase leukocyte activation, adhesion molecule synthesis, and pro-inflammatory cytokine production [13, 14].

So far, few studies with different results that investigate the relation of visfatin with chronic renal failure (CKD) stages and proteinuria have been published. One of the most important studies on this topic was conducted by Yılmaz et al. who included 406 non-diabetic patients with distinct stages of CKD and compared them to the control group. Visfatin levels were found to be elevated in stage-3, -4, and -5 patients, showing a negative correlation with GFR [15]; however, in our study, visfatin levels did not differ significantly among the study groups. In addition, no significant correlation was found between visfatin levels and GFR. However, diabetic patients were excluded from the study conducted by Yılmaz et al., whereas the population in our study was entirely

Table 1. Demographic data

Variable		Whole population (n=141)		Group I (n=37)		Group II (n=37)		Group III (n=34)		Group IV (n=33)		p
		n	%	n	%	N	%	n	%	n	%	
Gender	Male	58	41.2	15	40.6	18	48.6	13	38.2	12	36.3	0.730
	Female	83	58.8	22	59.4	19	51.4	21	41.8	21	63.7	
Age	Year ± SD	55.3±8.2		53.5±7.1		54.7±10		54.7±7.6		58.7±7.1		0.051
Duration of DM	Year ± SD	10.7±7.9		8.8±7.1		9.1±6.		11.8±9.3		13.5±7.7		0.036
BMI	Kg/m^2	30.5±5.1		29.2±5.0		32.2±5.5		30.2±4.8		30.9±4.9		0.085

Abbreviations: DM, Diabetes mellitus; BMI, Body mass index; SD, Standard deviation

Table 2. Hematological and biochemical data of patients according to groups

Variable		Group I	Group II	Group III	Group IV	p
White blood cell	mm^3	8.1±1.9	7.9±1.7	8.8±2.5	9.1±2.7	0.09
Hemoglobin	g/dl	13.4±1.3	13.4±1.2	12.8±1.4	11.1±1.5	<0.001
Hematocrit	%	40.6±3.5	41.1±3.6	39.1±4	34.1±4.8	<0.001
Mean cell volume	fl	86±5	85±4	86±5	86±3	0.677
Thrombocyte	$x1000/mm^3$	283±85	279±52	290±87	298±86	0.758
Ferritin	ng/ml	52.4±39.8	62.7±47	47.9±41.2	140.5±139.1	<0.001
Fasting blood glucose	mg/dl	189±81	192±92	212±89	208±95	0.621
HbA_{1c}	%	8.3±2.1	8.5±1.9	8.9±1.9	8.6±1.4	0.549
Urea	mg/dl	32.0±7.5	30.8±9.3	37.1±15.2	94.0±39.6	<0.001
Creatinine	mg/dl	0.72±0.14	0.76±0.15	0.87±0.26	2.2±1.0	<0.001
e-GFR	$ml/min/1.73m^2$	99±14	96±15	84±22	33±15	<0.001
Uric acid	mg/dl	4.7±1.5	4.8±1.1	5.4±1.8	6.3±1.2	<0.001
Sodium	mmol/L	138±3	138±3	138±3	138±3	0.945
Potassium	mmol/L	4.5±0.4	4.5±0.4	4.6±0.5	4.8±0.4	0.020
Calcium	mg/dL	9.7±0.5	9.7±0.5	9.6±0.5	9.4±0.6	0.139
Phosphorus	mg/dL	3.4±0.6	3.6±0.4	3.5±0.5	4.1±0.9	<0.001
Parathyroid hormone	pg/mL	47±19	54±20	59±33	138±146	<0.001
Total protein	g/dL	7.3±0.4	7.4±0.4	7.3±0.4	7.3±0.6	0.476
Albumin	g/dL	4.3±0.2	4.2±0.3	4.1±0.4	3.9±0.5	<0.001
Alanine aminotransferase	U/L	27±15	23±13	30±27	18±9	0.03
Aspartate aminotransferase	U/L	24±16	22±9	24±10	17±6	0.07
Total cholesterol	mg/dL	207±60	220±38	227±63	227±68	0.458
Low-density lipoprotein	mg/dL	129±48	135±34	140±51	143±58	0.641
High-density lipoprotein	mg/dL	45±10	42±9	43±10	42±9	0.521
Triglyceride	mg/dL	165±82	215±101	250±239	219±98	0.09
HOMA-IR		4.4±4.5	4.9±4.1	7.0±4.3	8.2±5.5	0.009
Micro-albuminuria	mg/day	10.1±9.8	89.4±68.2	525.1±280.7	1034±1893	<0.001

Abbreviations: GFR, Glomerular Filtration Rate; **HOMA-IR**, Homeostatic Model Assessment for Insulin Resistance

diabetic. In addition, unlike the study by Yilmaz et al., ESRD patients were not included in our study.

Kocelak et al. performed a study with 3023 elderly patients and did not show any relationship between visfatin levels and GFR, with similar findings observed in our study. In addition, although they divided patients into 2 groups according to GFR as patients with GFR below 60 or above 60 ml/min/m2, no significant difference could be found between the groups in terms of visfatin levels. However, they did not include diabetic patients either (16).

There are few studies that include diabetic patients and it is therefore difficult to drive any conclusion on

Table 3. Visfatin, IL-6, TNFα, and hsCRP levels in groups

Variable		Group I	Group II	Group III	Group IV	p
Visfatin	pg/ml	2.6±1.2	4.4±5.9	2.5±2.0	2.7±1.1	0.051
IL-6	pg/ml	4.2±2.5	8.0±8.1	6.3±6.9	9.1±10.9	0.103
TNFα	pg/ml	12.5±21.6	8,6±7,9	18,0±18,7	20.6±18.3	0.021
HsCRP	mg/L	0.46±0.42	0.48±0.36	0.92±1.18	0.80±0.92	0.064

Abbreviations: hsCRP, High sensitivity C-reactive protein; **IL,** Interleukin; **TNFα,** Tumor necrosis factor alpha

Table 4. Visfatin-related parameters in multivariate analysis in patients with and without macro-albuminuria

	Normal and micro-albuminuria			Macro-albuminuria		
Variable	B	Beta	p	B	Beta	p
Age	-0.106	-0.156	0.270	-0.077	-0.207	0.109
Gender	-0.001	-0.003	0.982	0.044	0.187	0.147
BMI	0.784	0.083	0.570	0.511	0.159	0.248
Total protein	-1.154	-0.158	0.269	0.043	0.012	0.928
IL-6	-0.068	-0.121	0.417	0.070	0.380	0.006
TNFα	0.006	0.037	0.791	-0.004	-0.098	0.435

Abbreviations: BMI: Body mass index; **hsCRP**, High sensitivity C-reactive protein; **IL,** Interleukin; **TNFα ,** Tumor necrosis factor alpha

the change of visfatin levels in diabetic patients. In a small cross-sectional study by Mahmoud et al. who compared 50 CKD patients to a control group consisting of 28 healthy subjects, the patients in the CKD group were grouped according to whether they were diabetic or not, no significant difference was found between the groups in terms of visfatin levels. Visfatin level was positively correlated with proteinuria and negatively correlated with GFR (17).

Axelsson et al. compared stage 3 to 5 CKD patients to control group in terms of visfatin levels and reported that visfatin levels were higher in stage-5 CKD patients compared to those in all other groups. The authors also concluded that visfatin levels were negatively correlated with GFR and positively correlated with IL-6 and hsCRP. Visfatin levels were similar in diabetic vs. non-diabetic patients (18).

The number of studies examining the relationship between proteinuria and visfatin level is also limited. In a study by Yılmaz et al., 85 type II-DM patients were compared to the control group and visfatin levels were found to be greater in the diabetic group. The study also examined the changes in visfatin levels by the degree of proteinuria and found that patients with proteinuria greater than 500 mg/day had higher visfatin levels than those with proteinuria less than 500 mg/day. In this study, a positive correlation was also found between visfatin levels and proteinuria (19). In our study, a positive correlation was found between albuminuria and visfatin levels only in patients with macro-albuminuria and GFR values above 60 ml/min/1.73m^2.

There are conflicting data in the literature regarding the relation between visfatin levels and obesity. Kang et al. reported that visfatin levels were positively correlated with body weight but had no relationship with BMI (20). Haider et al. found a decrease in visfatin levels following gastric surgery in obese patients. In other studies, higher visfatin levels were found in obese adolescent patients. In an experimental rat study, no relationship between visfatin levels and obesity could be demonstrated [21-23]. In our study, no correlation was found between visfatin levels and BMI.

Current literature findings respecting the association between visfatin levels and $HgbA_{1c}$ are conflicting. In some studies, visfatin levels in type II-DM were found to be associated with higher HbA_{1c} levels, whereas visfatin levels were found to be low in type I-DM and had a negative correlation with HbA_{1c} (24, 25). In our study, no correlation was found between visfatin levels and HbA_{1c}.

Visfatin has pro-inflammatory effects and it has been shown to induce the synthesis of IL-1b, TNFα, and IL-6 dose-dependently in a study of human monocytes. At high concentrations, visfatin was shown to induce the expressions of IL-10 and IL-1Ra (anti-inflammatory cytokines). It also increases the monocyte surface expression of CD54 (ICAM-1), CD40, and CD80, which are co-stimulatory molecules and important for T cell activation (26).

When the whole patient population was evaluated in our study, univariate analysis showed a positive correlation only between visfatin levels and IL-6. No more correlation was found between visfatin levels

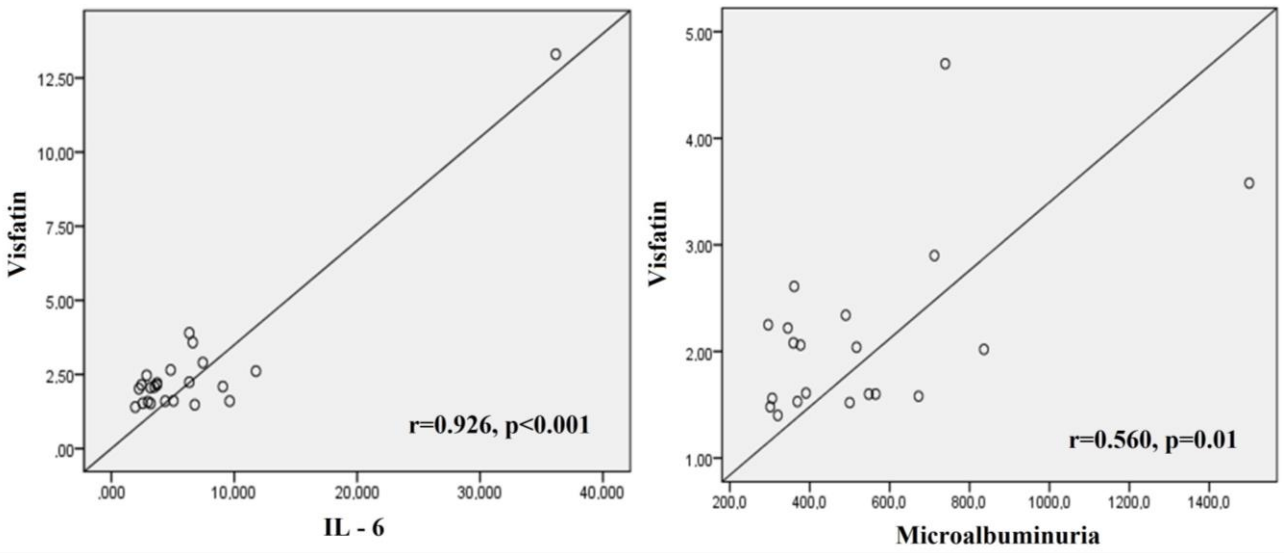

Fig. 1. The relation of visfatin with IL-6 and microalbuminuria in Group III

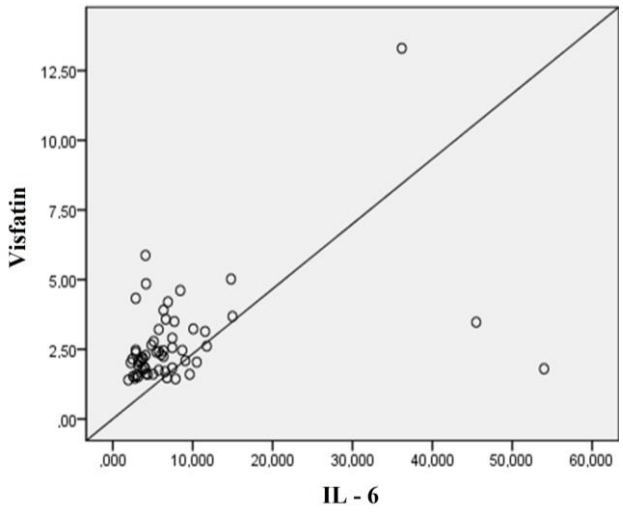

Fig. 2. The relationship between visfatin and IL-6 in macro-albuminuric patients

and other biochemical or inflammatory parameters (e.g., IL-1, TNFα, hsCRP). The number of studies analyzing visfatin in diabetic patients is extremely rare in the literature. Our study included only diabetic patients. In addition, the patients were grouped according to stages of DNP. However, the number of cases in each group was relatively low in our study. As a result, no clear data on the role of Visfatin in patients with DNP have yet been obtained.

There are different outcomes regarding the relation between visfatin and obesity, glucose metabolism disorders, renal dysfunction, proteinuria, and inflammation. In our study, visfatin was found to be closely associated with IL-6, which is an important marker of inflammation in patients with apparent DNP, namely macro-albuminuric patients.

Conflict-of-interest Statement: All authors declare that they have no conflicts of interest related to this article.

Funding source: None.

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