

Correlation Between Circulating Visfatin and Nitric Oxide Metabolites Levels in Patients With Diabetic Nephropathy

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Introduction. Diabetic nephropathy is one of the serious complications of diabetes mellitus. Visfatin is an intracellular enzyme with insulin-mimicking effects. It enhances the expression of endothelial nitric oxide (NO) synthase in renal cells. This study aimed to investigate serum levels of visfatin and NO metabolites in patients with diabetic nephropathy.

Materials and Methods. A total of 80 diabetic patients were enrolled and classified into nephropathic and non-nephropathic patients. Serum visfatin and insulin levels were estimated using an enzyme-linked immunosorbent assay, and NO metabolites were estimated using a colorimetric assay.

Results. Serum visfatin and NO metabolites levels were significantly elevated in the patients with diabetic nephropathy. Serum visfatin levels and NO metabolites were significantly higher in the nephropathic patients ($P = .003$; 95% confidence interval, 2.29 to 10.81; $P < .001$; 95% confidence interval, 3.14 to 9.46, respectively) as compared to the control group, whereas homeostatic model assessment-insulin resistance was significantly lower ($P = .02$; 95% confidence interval, -1.51 to -1.01). There was no correlation between body mass index, blood pressure, lipid profile, insulin, and glucose levels and serum visfatin and NO metabolites levels.

Conclusions. The results of this study demonstrated that there were high levels of visfatin and NO metabolites in patients with diabetic nephropathy. In addition, there was a positive correlation between visfatin and NO metabolites levels in nephropathic and non-nephropathic diabetic patients.

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INTRODUCTION

Diabetes mellitus (DM) has become an increasing health problem due to the increasing number of diabetic patients, high percentage of mortality associated with its complications, and high costs for these patients. The International Diabetes Federation reported that the number of diabetic adults has reached 415 million people globally in 2015. In the Middle East and North Africa, approximately 35.6

million people are currently suffering from DM. Diabetic patients are at a higher risk of developing DM complications, which include retinopathy, nephropathy, neuropathy, cardiovascular diseases, and diabetic foot.¹

Diabetes is one of the main risk factors for the development and progression of chronic kidney disease. It has been known that in 25% to 40% of patients with DM, diabetic nephropathy

is developed within 20 to 25 years.² Diabetic nephropathy is characterized by a glomerular filtration rate (GFR) less than 60 mL/min/1.73 m² and persistent albuminuria (> 300 mg/d or > 200 µg/min). Since the prevalence of type 2 DM is higher than that of type 1 DM, most of the nephropathic patients are clustered in the type 2 group.³

One of the factors that lead to the development of nephropathy is adipokine imbalance. In addition to the energy storage role, adipose tissue can act as an endocrine organ. It can secrete adipokines and affect many metabolic and inflammatory processes. In type 2 DM, the balance of some adipokines is corrupted and this in turn causes small blood vessel complications of DM, such as diabetic nephropathy.⁴

Visfatin is a multiple role-player adipokine which has an important role in inflammation, obesity, metabolic syndrome, endothelial cell function, angiogenesis, and cardiovascular diseases.⁵ Visfatin is a 52 kDa protein and is an intracellular enzyme which was first reported as pre-B cell colony enhancing factor. Later, due to involvement in biosynthesis, it was named nicotinamide phosphoribosyl transferase. In addition, it was described as a visceral fat derived hormone by Fukuhara and colleagues in 2005.⁶ Visfatin has also been reported to elevate renal fibrosis by increasing the activity of matrix metalloproteinase 2 and matrix metalloproteinase 9, which is a general feature of chronic kidney disease (CKD). It has been reported that mesangial cells in kidney can secrete visfatin as well as visceral fat cells, neutrophils, monocytes, macrophages, epithelial, and endothelial cells.⁵

High blood glucose stimulates synthesis of intracellular visfatin. Then visfatin stimulates glucose uptake by renal cells which activates some inflammatory pathways leading to injury in diabetic nephropathy. In high levels, visfatin causes synthesis of inflammatory cytokines including interleukin-6, interleukin-8, tumor necrosis factor- α , and interleukin-1 β , and also activates nuclear factor- κ B pathway. All these can lead to the expansion of inflammation in the body. Additionally, visfatin enhances the expression of vascular endothelial growth factor, vascular endothelial growth factor-2 receptor, and endothelial nitric oxide synthase (ENOS) in renal cells through the mitogen-activated protein kinase and Akt pathways.⁷

By the action of ENOS, nitric oxide (NO) is produced from L-arginine. Nitric oxide has a short half-life and quickly turns to its metabolites, nitrite and nitrate. With the help of NO, VEGF increases endothelial cell migration and proliferation and leads to disintegration of the endothelial cell matrix. Thus, all these factors cause angiogenesis in renal cells. The activity of ENOS is decreased in advanced cases of diabetic nephropathy. This decrease is due to the restriction of enzyme substrate, existing enzyme inhibitors like asymmetric dimethylarginine, activation of C protein kinase and increase of advanced glycation end products that cause decomposition of nitric oxide synthase mRNA and decrease its gene expression and deactivation of NO, which eventually leads to the reduction of ENOS activity. Following the reduction of enzymatic activity, angiogenesis does not occur properly. In addition, since NO has other effects like anti-inflammatory, anticoagulant, and anti-sclerosis effects, the presence of NO is necessary for stability of endothelial cell homeostasis. Visfatin causes activation of dimethylarginine dimethylaminohydrolase which leads to the hydrolysis of asymmetric dimethylarginine and increased NO levels.^{8,9}

Due to its radical nature and short half-life, the determination of NO metabolites is most often used as a predictor of NO production.¹⁰ Based on the effects of visfatin on NO, it is hypothesized that visfatin may be of relevance to nitric oxide production. In this study, we aimed to evaluate serum levels of visfatin and NO metabolites as an indicator of serum NO levels in nephropathic and non-nephropathic diabetic patients and to investigate the correlation of NO and visfatin in these patients.

MATERIALS AND METHODS

Participants

This study was conducted at the Drug Applied Research Center of Tabriz University of Medical Sciences and included 80 participants. The study protocol was approved by the local ethics committee of Tabriz University of Medical Sciences. Informed consent was obtained from all the participants. Forty of the participants (20 men and 20 women) with the mean age of 57.85 ± 5.63 years had diabetic nephropathy and were in CKD stages 3 and 4, and the remaining 40 were non-nephropathic diabetic

patients of matched sex and age (mean age, 56.95 ± 6.11 years). The second group was selected as the control group. Both groups were selected from patients who were referred to Imam Reza Hospital, Tabriz, Iran. All participants were identified as having diabetic nephropathy according to their medical history, estimated GFR and existence of kidney injury described by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines.¹¹ Participants who suffered from acute coronary syndrome, congestive heart failure, and primary hypertension, and those taking angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or insulin were excluded. The estimated GFR was calculated using the following formula as described by Levey and colleagues¹²:

$$\text{GFR} = (194 \times \text{serum creatinine}) - (1.094 \times \text{Age}) - (0.287 \times 0.739 \text{ (if female)}),$$

Homeostatic model assessment-insulin resistance (HOMA-IR) was calculated according to as follows:

$$\text{HOMA-IR} = \text{insulin} \times \text{glucose (mg/mL)} / 405$$

Sample Processing and Biochemical Analysis

Blood samples were obtained from all patients who were fasted for at least 10 hours. All the samples were centrifuged at 3000 g for 10 minutes and serum samples were divided into aliquots and stored at -70°C until analysis.

Nitric oxide metabolites were measured by colorimetric assay kit (Sigma Aldrich, USA) following the manufacturer's instruction.¹³ For this measurement, all serum samples were first deproteinated by centricon 10 (Amicon Ultra-4). Serum visfatin levels were estimated by an enzyme-linked immunosorbent assay kit (Sigma Aldrich, USA).¹⁴ Insulin levels were measured using an enzyme-linked immunosorbent assay kit (Monobind, USA). Other biochemical parameters were estimated by routine laboratory tests (Pars Azmoon, Iran).

Anthropometric Measurements

Weight, height, and hip and waist circumferences were estimated using the standard methods. The hip circumference was measured as the greatest circumference around the buttocks and waist circumference was measured halfway between the costal edge and iliac crest. The waist-hip circumference ratio was calculated by dividing the

waist circumference by the hip circumference. Body mass index was calculated as weight (kg) divided by squared height (m^2). Systolic and diastolic blood pressures were evaluated twice after the patients had rested for 15 minutes in a sitting position.

Statistical Analysis

All data were expressed as mean \pm standard deviation. The Kolmogorov-Smirnov test was used for assessment of the distribution of variables. The Pearson correlation coefficient test was used to test the correlation between visfatin, NO metabolites, and other parameters. Comparisons of variables between the controls and patients with diabetic nephropathy were determined using the Student *t* test. The Statistical Package for Social Science version 18 (SPSS Inc., Chicago, Illinois, USA) was used for data analysis. Two-sided *P* values less than .05 were considered significant.

RESULTS

Table 1 demonstrates the clinical and biochemical data of the controls and nephropathic patients. There were no significant differences between nephropathic and controls in terms of age, body mass index, heart rate, systolic and diastolic blood pressure, waist circumference, hip circumference, waist-hip circumference ratio, triglyceride level, total cholesterol level, high-density lipoprotein cholesterol levels, low-density lipoprotein cholesterol levels, fasting blood glucose, and insulin levels. The creatinine and urea levels were significantly higher in nephropathic patients in comparison with the control group ($P < .001$). The total protein and estimated GFR were significantly lower ($P < .001$) in nephropathic patient as compared to the control group.

Serum visfatin levels and NO metabolites were significantly higher in the nephropathic patients ($P = .003$; 95% confidence interval, 2.29 to 10.81; $P < .001$; 95% confidence interval, 3.14 to 9.46, respectively) as compared to the control group, whereas HOMA-IR was significantly lower ($P = .02$; 95% confidence interval, -1.51 to -1.01).

As demonstrated in Table 2, serum visfatin levels was positively correlated with levels of NO metabolites ($r = 0.506$; $P = .001$) and serum creatinine level ($r = 0.41$; $P = .007$) among the nephropathic patients. Whereas, there was a negative correlation between serum visfatin levels and estimated GFR

Table 1. Clinical and biochemical data of Patients*

Variable	Nephropathy Group	Control Group	P
Age, y	57.85 ± 5.63	56.95 ± 6.11	.496
Weight, kg	79.55 ± 12.62	75.05 ± 12.22	.11
Height, cm	165.45 ± 10.06	163.3 ± 9.4	.33
Body mass index, kg/m ²	29.02 ± 3.51	28.27 ± 4.96	.44
Duration of diabetes, y	9.9 ± 5.6	6.93 ± 3.13	.004
Systolic blood pressure, mm Hg	130 ± 11.58	128.3 ± 9.57	.46
Diastolic blood pressure, mm Hg	83 ± 10.9	82 ± 10.17	.67
Heart rate per minute	75.05 ± 9.9	78.35 ± 4.78	.06
Creatinine, mg/dL	2.57 ± 0.71	0.96 ± 0.2	< .001
eGFR, min/mL/1.73 m ²	26.13 ± 8.89	78.65 ± 16.44	< .001
Urea, mg/dL	49.44 ± 3.35	39.74 ± 3.06	< .001
Waist circumference, cm	106.28 ± 8.84	103.9 ± 9.91	.26
Hip circumference, cm	111.65 ± 7.34	109.25 ± 8.92	.19
Waist-hip circumference ratio	0.94 ± 0.05	0.94 ± 0.04	.86
Total protein, g/dL	5.62 ± 1.04	7.69 ± 0.71	< .001
High-density lipoprotein cholesterol, mg/dL	47.40 ± 8.33	45.75 ± 8.47	.38
Low-density lipoprotein cholesterol, mg/dL	111.83 ± 24.04	120.38 ± 23.19	.11
Triglyceride, mg/dL	206.55 ± 41.3	199.65 ± 33.14	.41
Cholesterol, mg/dL	193.53 ± 28.87	188.23 ± 31.73	.44
Nitric oxide metabolites, μM/mL	40.37 ± 8.41	34.07 ± 5.46	< .001
Visfatin, ng/dL	35.22 ± 11.58	28.66 ± 6.98	.003
Homeostatic model assessment-insulin resistance	3.31 ± 1.47	4.12 ± 1.68	.02
Glucose, mg/dL	148.8 ± 25.6	158.2 ± 40.5	.22
Insulin, μIU/mL	9.15 ± 4.35	11.09 ± 4.91	.06

*Data are expressed as mean ± standard deviation.

Table 2. Correlations Between Serum Visfatin and Nitric Oxide (NO) Metabolites and Other Parameters in Each Study Group*

Parameter	Nephropathy Group		Control Group	
	Visfatin	NO Metabolites	Visfatin	NO Metabolites
Visfatin	...	0.50 (.001)	...	0.31 (.04)
NO metabolites	0.50 (.001)	...	0.31 (.04)	...
Estimated glomerular filtration rate	-0.32 (.04)	-0.22 (.16)	0.23 (.14)	-0.11 (.48)
Creatinine	0.41 (.007)	0.18 (.25)	-0.306 (.05)	0.06 (.70)
Homeostatic model assessment-insulin resistance	0.16 (.30)	-0.08 (.58)	-0.12 (.44)	-0.12 (.45)
Insulin	0.19 (.23)	0.02 (.87)	-0.19 (.23)	-0.10 (.50)
Glucose	0.03 (.83)	-0.18 (.24)	0.25 (.10)	-0.44 (.78)
Low-density lipoprotein cholesterol	0.05 (.74)	-0.07 (.62)	0.75 (.64)	-0.38 (.81)
High-density lipoprotein cholesterol	0.06 (.67)	0.96 (.55)	-0.11 (.47)	0.95 (.55)
Systolic blood pressure	0.1 (.50)	-0.21 (.89)	-0.14 (.93)	-0.24 (.13)
Diastolic blood pressure	-0.11 (.48)	-0.18 (.26)	0.07 (.64)	-0.08 (.62)
Body mass index	-0.02 (.86)	0.01 (.94)	-0.11 (.47)	-0.19 (.23)

*Values are correlation coefficients (P values).

($r = -0.302$; $P = .04$) among the nephropathic patients. Furthermore, there was a positive correlation between serum visfatin levels and NO metabolites ($r = 0.31$; $P = .04$) among the controls.

DISCUSSION

Since DM has become a global health problem, and diabetic nephropathy has become a serious problem in Iran as well as around the world. This

study demonstrated that serum levels of visfatin and nitric oxide metabolites are elevated in patients with diabetic nephropathy in comparison with non-nephropathic patients. In this study, it was shown that the serum levels of visfatin are positively correlated with serum levels of NO metabolites. According to some studies, renal glomerular mesangial cells can synthesize visfatin, which can be upregulated by elevated glucose

stimulation. On the other hand, when GFR was low, the clearance of visfatin decreased, and therefore, serum visfatin levels were elevated in nephropathic condition. Other previous studies also confirm that there are high levels of serum visfatin in diabetic nephropathy.^{5,7,15}

The associations of visfatin with different stages of CKD have been studied by several researchers. This study included patients who were in CKD stages 3 or 4. Yilmaz and colleagues¹⁶ carried out their research on all the CKD stages. They found that there is no significant difference in visfatin levels between the controls and patients with stages 1 and 2 CKD; however, high levels of visfatin was found in patients who were in stages 3 to 5 as compared to patients who were in stages 1 and 2 and controls. In addition, CKD patients of stages 3 to 5 were studied by Axelsons and coworkers,¹⁷ and serum levels of visfatin were higher in patients in CKD stage 5 than in those in CKD stages 3 to 4 or healthy controls. It was found that high levels of visfatin can lead to progressive renal injury in stages 3 and 4 of CKD patients.

Nitric oxide has protective effects on renal cells, it can reduce inflammation, improve angiogenesis, dilate arterioles, and improve endothelial cell function. Also, in several studies, lower serum NO metabolites levels were reported in all stages of CKD¹⁸; significantly higher levels of NO end products in serum of patients with diabetic nephropathy were found in the present study. This may be due to a generalized increased NO synthesis all over the body which confirms that nephropathy is related to endothelial dysfunction. Additionally, visfatin can increase the production of NO in human endothelial cells by enhancing the expression and activity of endothelial nitric oxide synthase. In addition, visfatin can hydrolyse asymmetric dimethylarginine, which is an ENOS inhibitor by dimethylarginine dimethylaminohydrolase.⁹ High levels of serum NO metabolites was reported in early stages of patients with diabetic nephropathy.¹⁹ However, in the current study, despite higher serum levels of NO, there was no improvement in nephropathic conditions and all patients with diabetic nephropathy who had elevated NO metabolites serum levels were in stages 3 or 4. It is concluded that NO alone cannot improve nephropathic condition and there is a need for other destructive factors which were not examined

in this study.

In this study, serum creatinine, urea, NO metabolites and visfatin levels were higher in patients with diabetic nephropathy, and estimated GFR, serum total protein, and HOMA-IR were higher in the controls. It is assumed that high HOMA-IR could be due to the lower levels of visfatin in non-nephropathic patients as compared to nephropathic ones. This is due to the fact that visfatin is an adipokine, which has an insulin mimicking effect. It can bind to insulin receptors at a different site from insulin and decrease the glucose released from the liver, and in peripheral tissues, leading to the stimulation of glucose utilization.²⁰ Many studies reported that there was no correlation between visfatin and insulin sensitivity,^{21,22} whereas some other studies demonstrated that there was a positive correlation between serum visfatin levels and HOMA-IR.^{23,24} Similar to previous studies, there was no association between serum visfatin levels and HOMA-IR in both groups. Further molecular studies are needed to elucidate these findings.

It was also observed that there was a negative correlation between serum visfatin and the estimated GFR among patients with diabetic nephropathy. This is in line with some previous reports and findings.¹³⁻¹⁷ Moreover, there was a positive correlation between serum visfatin levels and serum creatinine levels in patients with diabetic nephropathy. Thus, it is hypothesized that the high levels of visfatin could be due to a decline in GFR, and visfatin levels may be influenced by kidney function. These are in accordance with the findings of previous studies.²⁵

The limitations of this study included the method used for measurement of insulin sensitivity; the HOMA formula was applied, which is only an estimation and not as accurate as the glucose clamp test. Another limitation was the lack of urine analyses, for example, levels of excretory visfatin, nitric oxide metabolites, and protein. It is also important to mention that all evaluations and investigations of this study were done before nephropathic patients progressed to the end stage.

CONCLUSIONS

Results of the present study demonstrated that in patients with diabetic nephropathy, serum visfatin levels and NO metabolites were higher than in type 2 diabetic patients. Additionally, there

was a positive correlation between serum visfatin levels and NO metabolites in both groups. Further studies, with larger sample sizes, are required to corroborate diagnostic and treatment features of using serum visfatin and nitric oxide metabolites in diabetic nephropathy.

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CONFLICT OF INTEREST

None declared.

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