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Original Article

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Is Serum Vasohibin-1 Level Associated with the Development of Kidney Disease in Diabetic Patients?

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ABSTRACT

Objective: Glomerular neoangiogenesis contributes to increased glomerular filtration rate in patients with diabetic kidney disease. Vasohibin-1 is a neoangiogenesis inhibitor. We aimed to evaluate serum vasohibin-1 levels of diabetic patients with and without diabetic kidney disease.

Methods: A total of 105 diabetic patients and 35 healthy controls were included in the study. Diabetic patients with estimated glomerular filtration rate <60 mL/min/1.73 m^2 and/or those who had persistent proteinuria (>200 mg/g) measured by urinary protein/creatinine ratio were diagnosed as diabetic kidney disease patients if they do not have any other known kidney diseases or findings suggesting another kidney disease. Serum creatinine, estimated glomerular filtration rate, protein/creatinine ratio, and vasohibin-1 levels were recorded.

Results: Systolic blood pressure and protein/creatinine ratio were higher in diabetic patients than in healthy controls, and age, sex, and estimated glomerular filtration rate were similar. Diabetic patients have slightly lower but statistically nonsignificant serum vasohibin-1 levels than healthy controls. Patients with diabetic kidney disease had higher protein/creatinine ratio, lower estimated glomerular filtration rate, and long-standing diabetes compared to diabetic patients without kidney disease. Serum vasohibin-1 levels were similar between patients with and without diabetic kidney disease. There was no correlation between serum vasohibin-1 levels and estimated glomerular filtration rate or protein/creatinine ratio. In logistic regression analysis, vasohibin-1 was not associated with diabetic kidney disease.

Conclusion: We showed that diabetic patients have slightly lower vasohibin-1 levels than healthy subjects but there was no difference between diabetic patients with and without kidney disease in terms of serum vasohibin levels. Because vasohibin-1 exhibits its antiangiogenic properties by acting via autocrine-paracrine pathways, local vasohibin activity at the tissue level may be more important than the circulating levels.

Keywords: Diabetic kidney disease, proteinuria, vascular endothelial growth factor-A, vasohibin-1

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INTRODUCTION

Diabetic nephropathy (DN) continues to be the most important cause of kidney failure worldwide.[1] In the early stages of nephropathy, glomerular hypertrophy and increased glomerular filtration rate (GFR) are seen. Proteinuria, mesangial matrix increase, and basement membrane thickening developed over time and eventually led to glomerular sclerosis.[2] Numerous molecules such as renin-angiotensin system (RAS), advanced glycosylation end products, fibrogenic transforming growth factor 1 (TGF-1), and insulin-like growth factor 1 (IGF-1) play a role in this process.[3,4]

Neoangiogenesis is observed in the development of nephropathy as well as development of retinopathy among diabetic rats.[5,6] Animal studies with type 1 and type 2 diabetic rodents revealed an increase in the total length of glomerular capillaries and new glomerular capillary formation.[5,6] This new vessel formation contributes to increased glomerular surface area and increased GFR in the early stages of nephropathy and hence accelerates the development of nephropathy. Vascular endothelial growth factor A (VEGF-A), the key molecule of neoangiogenesis, is known to contribute to this process. Overexpression of VEGF-A leads to mesangial matrix increase and basement membrane thickening in rat kidneys similar to DN.[7] Vascular endothelial growth factor A and VEGF-A receptor levels were found to be high in DN models.[8,9] Numerous anti-VEGF-A therapies are being tried to treat DN.

Vasohibin-1 is a peptide, consisting of 365 amino acids, produced mainly by endothelial cells and exhibits anti-angiogenic properties by acting via autocrine–paracrine pathways.[10,11] Its molecular weight is 44 kDa, and Western blotting showed that there are 4 more bands of 42, 36, 34, and 27 kDa.[11] It is considered as a negative feedback regulator of angiogenesis.[10] Increasing the vasohibin-1 expression by adenoviral vector transfer in type 1 and type 2 diabetic mice led to an improvement in microalbuminuria, a decrease in increased GFR, and an improvement in pathological changes.[12,13] Vasohibin-1 expression has been shown to be decreased in rat kidney with diabetic kidney disease (DKD).[14] However, unfortunately, there is little research on the relationship between vasohibin-1 levels and the existence of DN in humans. The aim of this study is to evaluate serum vasohibin-1 levels of diabetic patients with and without kidney disease.

METHODS

This cross-sectional study was conducted at nephrology and endocrinology outpatient clinics of Kahramanmaraş Sütçü İmam University Faculty of Medicine, Turkey. One hundred five patients over 18 years old of age, who were already followed with the diagnosis of type 1 or type 2 diabetes mellitus (DM) and 35 healthy controls were included in the study. Type 1 diabetic patients with a history of diabetes less than 5 years and patients under 18 were excluded from the study.

MAIN POINTS

- Diabetic patients have slightly lower serum vasohibin-1 levels compared with healthy subjects.
- Patients with diabetic kidney disease have higher proteinuria and lower estimated glomerular filtration rate than diabetic patients without kidney disease but with similar vasohibin-1 levels.
- Vasohibin-1 level is not associated with important markers of kidney disease such as proteinuria and estimated glomerular filtration rate but is inversely correlated with systolic blood pressure.

Also the patients who have active malignancy or a history of malignancy, an active infection or kidney disease other than related to DM (such as acute or chronic glomerulonephritis, polycystic kidney disease, amyloidosis, nephrolitiasis, acute or chronic interstitial nephritis, etc.) and patients who were kidney transplant recipients were excluded from the study because it is known that some malignancies and infections may affect serum vasohibin-1 levels. To exclude other kidney diseases such as polycystic kidney disease, renal masses, and nephrolithiasis kidney imaging by ultrasonography, and urinary sediment were examined in all patients. The presence of diabetic retinopathy, coronary artery diseases, peripheral artery disease, diabetic neuropathy, hypertension (HT) and information of the duration of DM, oral antidiabetic agents, or insulin usage were obtained from patients' medical records. Fundoscopic examination of the patients was performed to investigate the presence of diabetic retinopathy by a single ophthalmologist if retinopathy examination was not performed within 1 year. The patients' body weight and height were measured and body mass index (BMI) was calculated by dividing the body weight (kg) of the patients by the square of their height (meters).

We diagnosed DKD if a patient has type 2 diabetes or longstanding type 1 diabetes for at least 5 years with persistent significant proteinuria and/or low eGFR (<60 mL/min/1.73 m^2). If the patient had findings that implicate the existence of other kidney diseases such as rapidly decreasing GFR, rapidly increasing proteinuria, refractory HT, active urinary sediment, signs of other systemic diseases, and a significant decline in GFR within 2-3 months after starting angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy, he or she was not defined as DKD and not included in the study.[15-17]

To define DKD, we used urinary protein/creatinine ratio (PCR) from spot urine sample which was measured from the first urine in the morning. Estimated GFR (eGFR) of patients were calculated using the CKD-EPI formula from serum creatinine values.[18] We retrospectively reviewed the patients' laboratory records for previous PCR and serum creatinine values to confirm that proteinuria and low eGFR were persistent for more than 3 months.

For the control group, 35 healthy subjects who matched with diabetic patients group in terms of age and gender were recruited from the hospital staff. Fasting blood glucose, HbA1c (glycated hemoglobin), serum creatinine (Cr), Na, K, albumin, uric acid (UA), low-density lipoprotein cholesterol, and triglyceride levels of the patients were measured by routine biochemical methods from the blood samples taken at 8:00 AM following a fasting period of around 8 hours. Two milliliters of blood samples were taken at the same time to determine the serum vasohibin-1 level, centrifuged at 3000 rpm for 5 minutes, and the separated serums were stored at -80 °C. Serum vasohibin-1 levels were measured by the ELISA method using "Human Vasohibin-1 ELISA Kit" (Lot: 30211832);

afterward, all serums were thawed simultaneously at room temperature in accordance with the instructions of the manufacturer. The measuring range of the kit was 0.156-10 ng/mL. The kit's intra-assay precision was ≤8%. The inter-assay precision was ≤12%. Written informed consent was obtained from all patients to participate in the study. Ethical approval was obtained from the Kahramanmaraş Sütçü İmam University local ethics committee on November 07, 2018, with resolution number 29 and session number 2018/20.

Statistical Analysis

We used Statistical Package for Social Sciences software 22.0 (IBM Corp., Armonk, NY, USA) for statistical analysis. The data obtained by measurement were expressed as mean ± standard deviation (SD), and the data were obtained by counting as numbers or ratios. Distribution analysis of continuous data was evaluated with Kolmogorov–Smirnov and Shapiro–Wilk tests. In the comparison of the 2 groups, for the data obtained from measurements, the *t*-test was used if the data matching the normal distribution, and the Mann–Whitney *U*-test was used if the data were not matching the normal distribution. Correlation analysis of continuous data was evaluated with Pearson or Spearman correlation analysis according to the distribution of data. Any *P* value <.05 was considered statistically significant.

Table 1. Comparison of Diabetic and Healthy Patients

	DM n = 105	Healthy n = 35	*P*
Age (years)	50.3 ± 12.1	47.2 ± 6	.12
Sex (M)%	43.8	56.4	.2
Type of DM (type 1/type 2)%	17.1/82.9	–	
DM duration (years)	9.4 ± 7.4	–	
BMI (kg/m^2)	30.3 ± 7.2	29.2 ± 3.8	.2
Hypertension (%)	46.7%	–	
Patient receiving insulin (%)	55.2	–	
Neuropathy (%)	7.6	–	
DKD (%)	34.3	–	
Retinopathy (%)	15.2	–	
Coronary disease (%)	16.2	–	
PCR (mg/g)	415.9 ± 755.7	92.3 ± 21.4	<.001
SBP (mmHg)	128.8 ± 16.5	123.5 ± 8.7	.01
DBP (mmHg)	77.6 ± 10.7	78.9 ± 7.0	.4
eGFR (mL/min/1.73 m^2)	102 ± 25.4	103.7 ± 11.9	.4
Creatinine (mg/dL)	0.8 ± 0.6	0.75 ± 0.1	.6
Fasting blood glucose (mg/dL)	175.4 ± 65.2	93.6 ± 8.2	<.001
HbA1c (%)	8.5 ± 1.8	–	
Albumin (gr/dL)	4.2 ± 0.4	4.4 ± 0.2	.03
Uric acid (mg/dL)	5.0 ± 1.6	4.8 ± 1.2	.6
LDL cholesterol (mg/dL)	115 ± 38.3	144.3 ± 33.4	<.001
TG (mg/dL)	175.2 ± 90	138.5 ± 66.3	.03
Vasohibin 1 (pg/mL)	321.46 ± 56.48	350.1 ± 101.4	.1

BMI, body mass index; DBP, diastolic blood pressure; DKD, diabetic kidney disease; eGFR: estimated glomerular filtration rate with CKD-EPI equation; LDL, low-density lipoprotein; PCR, urinary protein/creatinine ratio; SBP, systolic blood pressure; TG, triglyceride.

RESULTS

Of the 105 diabetes patients included in the study, 17.1% had type 1 diabetes and 82.9% had type 2 diabetes. Forty-six percent of DM patients had HT. Seven point six percent of DM patients had neuropathy, 15.2% had retinopathy and 16.2% had coronary artery disease. We diagnosed DKD in 34.3% of all diabetic patients. There is not any significant difference between diabetic patients and healthy controls in terms of age, gender distribution, BMI, and eGFR (*P* > .05 for all). Systolic blood pressure (SBP) (128.8 ± 16.5 mmHg vs. 123.5 ± 8.7 mmHg *P* = .01), PCR (415.9 ± 755.7 mg/g vs. 92.3 ± 21.4 mg/g; *P* < .001), and

Table 2. Comparison of Diabetic Patients With and Without Kidney Disease

	DKD n = 36	Without DKD n = 69	*P*
Age (years)	51.5 ± 11.1	49.8 ± 12.7	.5
Sex (M)%	30.6/69.4	50.7/49.3	.07
Type of DM (type 1/type 2)%	16.7/83.3	17.4/82.6	1.0
DM duration (years)	11.5 ± 8.7	8.3 ± 6.5	.057
BMI (kg/m^2)	32.0 ± 8.3	29.4 ± 6.4	.08
PCR (mg/g)	956.81 ± 1077.75	116.45 ± 39.6	<.001
SBP (mmHg)	132.7 ± 19.4	126.8 ± 14.5	.07
DBP (mmHg)	78.4 ± 10	77.2 ± 11	.5
eGFR (mL/min/1.73 m^2)	90.3 ± 35.5	108.2 ± 15	.06
Creatinine	1.03 ± 1.07	0.66 ± 0.16	.05
Fasting blood glucose	185.9 ± 49.6	170.0 ± 71.7	.01
HbA1c (%)	9.0 ± 2.1	8.2 ± 1.6	.06
Albumin (g/dL)	4.0 ± 0.4	4.3 ± 0.2	<.001
Uric acid (mg/dL)	5.4 ± 1.8	4.8 ± 1.4	.09
LDL (mg/dL)	112.8 ± 37.5	116.2 ± 38.9	.7
TG (mg/dL)	192.5 ± 85.4	166.1 ± 91.6	.08
Vasohibin 1 (pg/mL)	325.55 ± 55.3	319.32 ± 57.3	.6

BMI, body mass index; eGFR, estimated glomerular filtration rate with CKD-EPI equation; DBP, diastolic blood pressure; DKD, diabetic kidney disease; DM, diabetes mellitus; LDL, low-density lipoprotein; PCR, urinary protein/creatinine ratio; SBP, systolic blood pressure; TG: triglyceride.

triglyceride values (175.2 ± 90 mg/dL vs. 138.5 ± 66.3 mg/dL; *P* = .03) of diabetic patients were higher than those of healthy controls, while their albumin (4.2 ± 0.4 g/L vs. 4.4 ± 0.2 g/L; *P* = .03) and LDL cholesterol (115 ± 38.3 mg/dL vs. 144.3 ± 33.4 mg/dL; *P* < .001) levels were lower (Table 1). Although serum vasohibin-1 levels were lower in diabetic patients than in healthy controls, this difference was not statistically significant (321.46 ± 56.48 pg/mL vs. 350.1 ± 101.4 pg/mL; *P* = .1).

Age, sex, BMI, eGFR values, SBP, and diastolic blood pressure (DBP) of 36 patients with DKD were not significantly different from those without kidney disease (*P* > .05 for all). Mean protein excretion of patients with DKD was 956.81 ± 1077.75 mg/g. Serum vasohibin-1 levels in patients with DKD were not different from those without kidney disease (325.55 ± 55.3 pg/mL vs. 319.32 ± 57.3 pg/mL; *P* = .6) (Table 2). When the analyses were repeated excluding type 1 diabetes patients, the results did not change. Diabetic patients with and without kidney disease and healthy control groups' serum vasohibin-1 levels are presented in Figure 1.

No significant correlation was found between the amount of proteinuria and serum vasohibin-1 levels in any of the groups (Table 3). The vasohibin-1 levels only in patients with DKD were moderately inversely correlated with SBP (*P* = .01 *r* = -0.4) (Figure 2). Also, the vasohibin-1 levels in patients with retinopathy were not different from those without retinopathy (data not shown). Logistic regression analysis revealed that only the duration of DM was associated the development of kidney disease (B: 0.08, *P* = .03, odds ratio (OR) = 1.09), but serum vasohibin-1 level was not associated with the development of kidney disease (*P* = .87) (Table 4).

DISCUSSION

In this study, we demonstrated that the serum vasohibin-1 levels in patients with clinically diagnosed DKD were not different from those of diabetic patients without kidney disease and healthy subjects. We also demonstrated that serum vasohibin-1 levels were not associated with clinical or laboratory findings related to DKD such as daily protein excretion and GFR.

It is well known that there is an increase in GFR in the early stages of diabetes. In addition to hemodynamic factors, glomerular neoangiogenesis contributes to this increase. Abnormal vascular structures have been described in the glomeruli in both rats and humans with DN.[5,6,19-22] Moreover, in rodents, an increase in glomerular filtration surface area due to slight elongation in new generated and also the existing capillaries has been shown.[5,6]

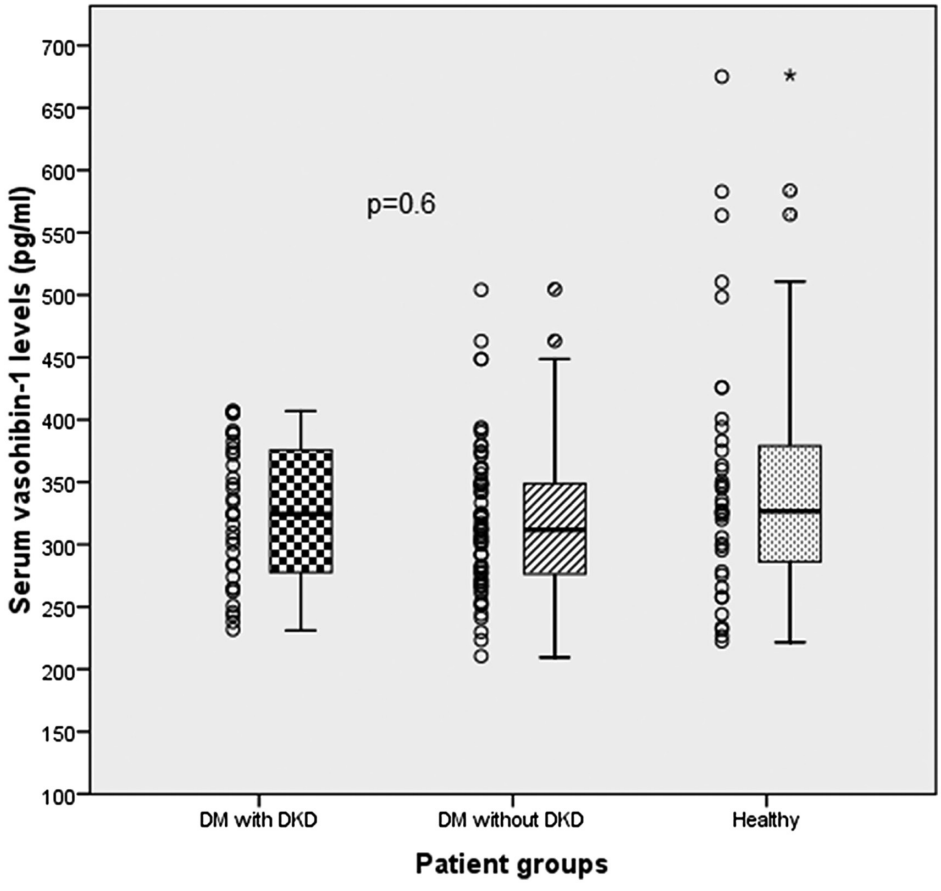

Figure 1. Dot-plot and box-plot graphics of serum vasohibin-1 levels of patients groups'.

Table 3. Correlations of Vasohibin 1 and Various Parameters in All 3 Groups

	Vasohibin-1					
	DKD		Without DKD		Healthy	
	r	*P*	*r*	*P*	*r*	*P*
Age	0.01	.9	0.1	.1	0.05	.7
eGFR	-0.05	.7	-0.14	.2	-0.05	.7
PCR	0.09	.5	0.01	.8	-0.1	.4
SBP	-0.4	.01	-0.009	.9	0.02	.8
DBP	-0.1	.3	-0.05	.6	0.05	.7
Albumin	-0.2	.2			-0.004	.9
Uric acid	-0.08	.6	0.04	.6	-0.1	.5
HbA1c	0.1	.4	-0.04	.7	–	–
BMI	-0.08	.6	-0.07	.5	-0.06	.6

BMI, body mass index; DBP, diastolic blood pressure; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate with CKD-EPI equation; SBP, systolic blood pressure.

Table 4. Factors Affecting the Development of Nephropathy in the Diabetic Patient Group (Logistic Regression)

	B	*P*	Odds Ratio	95% CI
Age	-0.008	.80	0.99	0.93-1.05
Gender	-0.75	.20	2.1	0.66-6.81
DM duration	0.084	.03	1.09	1.00-1.18
Type of DM (Type 1 or 2)	-0.22	.82	0.80	0.10-6.19
Vasohibin-1	<0.001	.87	0.99	0.99-1.00
SBP	-0.009	.64	0.99	0.95-1.03
Uric acid	0.23	.20	1.26	0.88-1.80
LDL cholesterol	-0.1	.20	0.99	0.97-1.00
BMI	0.04	.30	1.04	0.96-1.13

BMI, Body mass index; DM, diabetes mellitus; LDL, low-density lipoprotein; SBP: systolic blood pressure.

Angiogenesis is a physiological event that is defined as the formation of new vessels from existing vessels and is regulated by the balance between proangiogenic and antiangiogenic factors. The most important proangiogenic agent is VEGF-A. It is known that there is an increase in levels of VEGF-A, and its receptor VEGFR-2, in both humans with DN and animal experiments.[8,9,23,24] In experimental models, overexpression of VEGF-A has been

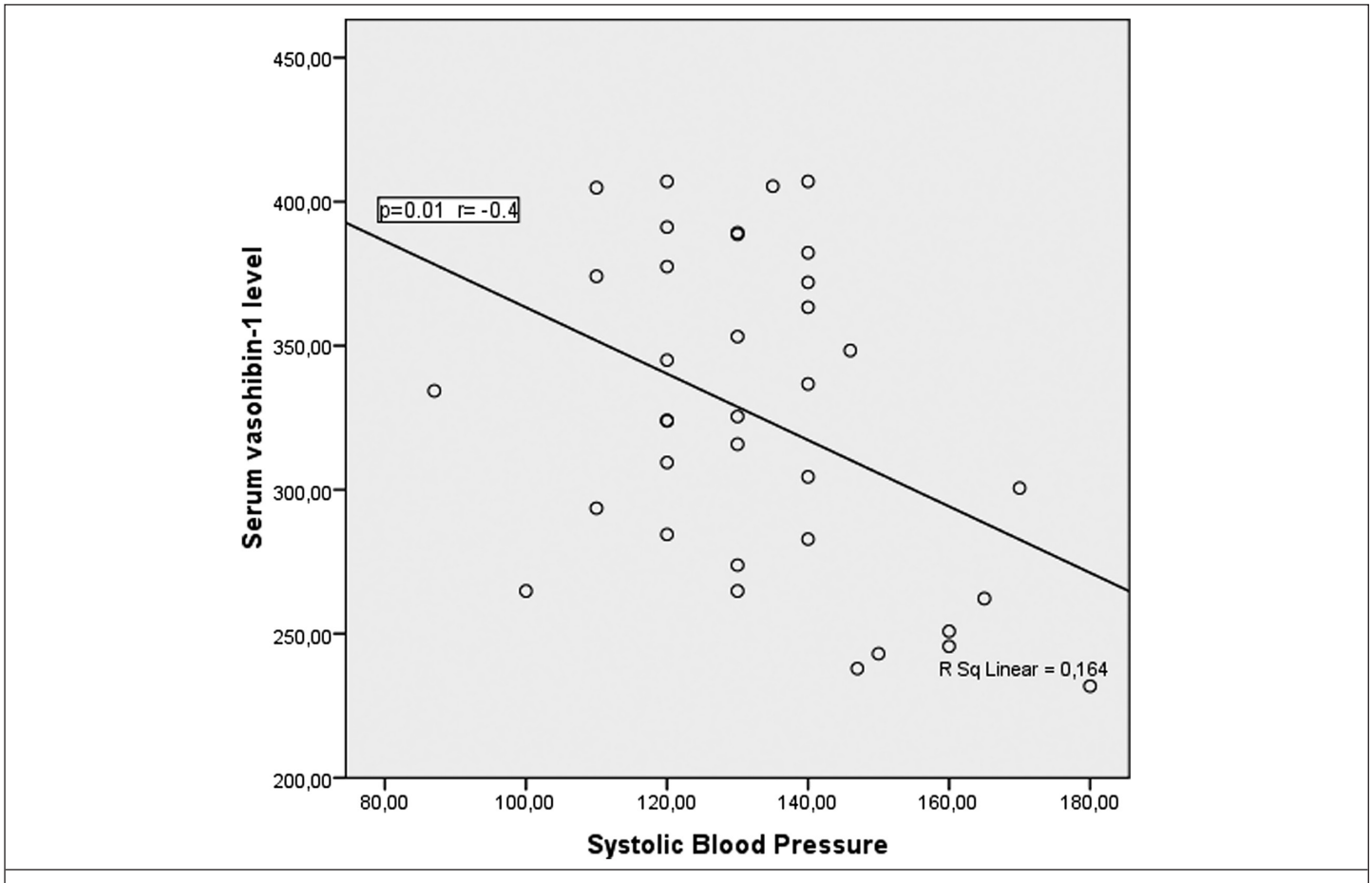

Figure 2. Correlation graphic between SBP and serum vasohibin-1 level of patients with DKD. DKD, diabetic kidney disease; SBP, systolic blood pressure.

shown to lead to basal membrane thickening and mesangial expansion similar to DN.[7] On the other hand, VEGF-A not only stimulates angiogenesis but also shows an increase in vascular permeability and chemotactic properties for monocytes.[25,26]

Vasohibin-1 is an antiangiogenic factor discovered for the first time during cDNA microarray assays to detect gene upregulation occurring against VEGF-A administration. It is synthesized by endothelial cells and acts as a negative feedback regulator that inhibits angiogenesis. Hence, vasohibin-1 can be expected to antagonize the deleterious effects of VEGF-A in the development of DN and hence prevent nephropathy. In type 1 diabetic mice, treatment with vasohibin-1 expressing adenoviral vector increased serum vasohibin-1 levels, resulting in a significant reduction in pathological changes, such as renal hypertrophy, glomerular hypertrophy and hyperfiltration, albuminuria, type 4 collagen deposition, and mesangial enlargement.[12] Also inflammatory cell infiltration, TGF B1 level, and MCP levels decreased. Treatment with vasohibin-1 resulted in a reduction in the number of receptors for high glucose-induced TGF beta, MCP-1, and advanced glycosylation end products in cultured mesangial cells. The same authors obtained similar results in obese type 2 diabetic mice and also demonstrated that treatment with vasohibin-1 reduced VEGF-A expression in podocytes incubated in a high glucose medium.[13] Vasohibin-1 expression has been shown to be decreased in rat kidney with DKD.[14] On the other hand, nephropathic changes due to streptozotocin-induced DM, such as diabetes-induced mesangial matrix enlargement, inflammatory infiltration, and albuminuria, were more severe in vasohibin-1 gene heterozygous knockout mice than in vasohibin-1 wild-type mice.[27] These findings suggest that vasohibin-1 possesses inhibitory properties against diabetic changes not only through antiangiogenic pathways but also through direct effect on mesangial cells and inflammatory cascade.

Unfortunately, the relationship between vasohibin-1 and DKD has not been adequately studied in humans. Recently, in a unique human study that investigates serum vasohibin-1 levels in diabetic patients, Ren et al have shown that ACR positively correlated with serum vasohibin-1 levels in 697 type 2 DM patients. They demonstrated in diabetic patients that those with macroalbuminuria had higher levels of vasohibin-1 than those with microalbuminuria, and that those with microalbuminuria had higher levels of vasohibin-1 than healthy individuals.[28] In our study, we could not demonstrate such a relationship between the presence and severity of proteinuria, and serum vasohibin-1 levels. During angiogenesis, vasohibin-1 is secreted from endothelial cells in the termination zone, which inhibits excessive vessel formation. Vasohibin-1 has autocrine and paracrine effects on tissue locally. In our study, the most plausible reason for the lack of correlation between clinical kidney disease parameters and serum vasohibin-1 levels was that the local paracrine effects of vasohibin-1 may be more important than the vasohibin-1 levels in the blood. The systemic and local activity of vasohibin-1 may be different, similar to the difference between systemic and tissue-level RAS activity. Hinamoto et al[29] evaluated the kidney biopsy findings and serum vasohibin-1 levels of 67 patients with CKD caused mostly by etiologies other than DN and 22 healthy control patients. Their results showed that serum vasohibin-1 levels were inversely correlated with SBP, DBP, and age and were not associated with GFR and proteinuria, suggesting that high urine and serum vasohibin-1 levels were associated with poor kidney outcomes. In our study, serum vasohibin-1 levels were inversely correlated with SBP in patients with DKD; however, we did not find any significant relationship between vasohibin-1 levels and other parameters such as age, sex, GFR, and proteinuria. In logistic regression analysis, vasohibin-1 was not associated with the development of kidney disease. On the other hand, cisplatin-induced acute kidney injury in vasohibin-1 knockout mice has been shown to be more severe than in wild-type mice.[30] It was observed in kidney biopsies taken from patients with kidney disease that vasohibin-1 was expressed in glomerular crescent and interstitial inflammatory cells, as well as in endothelial cells.[31] This finding suggests that vasohibin-1 may be associated with the progression of inflammation and kidney damage and that the kidneys respond to cellular stressors with an increase in vasohibin-1 expression.

Our study has some limitations. First, in this study we did not perform kidney biopsy because the diagnosis of DKD is usually a clinical diagnosis, but the absence of proteinuria does not mean that there are no histologically nephropathic changes in the kidney. There is no single universally valid definition of DN. Nowadays, the term DKD has started to be used instead of DN in order to include patients with reduced GFR without proteinuria. All around the world, the diagnosis of DKD is almost always based on clinical and laboratory findings with the exclusion of other possible kidney diseases without performing a kidney biopsy. Second, although studies show that the results of PCR and ACR are highly correlated, current guidelines use ACR for DKD diagnosis. We recruited patients with high urinary protein concentration rather than patients with moderate albuminuria. Therefore, early stage DKD patients are underrepresented. We had measure total protein in spot urine since albuminuria measurements were not available in our hospital. Therefore, we compulsorily used PCR instead of urinary albumin/creatinine ratio (ACR) to define significant proteinuria. Although current guidelines use ACR for DN diagnosis, studies show that the results of PCR and ACR are highly correlated.[32] According to the 2002 chronic kidney disease (CKD) guideline of KDOQI, PCR above 200 mg/g in a spot urine sample was define as significant proteinuria.[33] Third, evaluation of vasohibin-1 activity at tissue level may yield different results. Finally, our study was conducted with a relatively small number of patients. We showed that diabetic patients have slightly lower vasohibin-1 levels but it was not statistically significant. This difference may reach a more significant magnitude with larger patient numbers. Larger studies in which more patients are included are needed.

CONCLUSION

In this study, we showed that serum vasohibin-1 levels in DKD patients were not different from healthy individuals and diabetic patients without kidney disease. There is not significant number of studies on this subject and further studies are needed.

Human and Animal Rights: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics Committee Approval: Ethical approval was obtained from the Kahramanmaraş Sütçü İmam University local ethics committee (Date: November 7, 2018, Decision No: 2018/20).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - O.A.; Design - O.A.; Supervision - O.A.; Resources - D.T.S., M.S., O.A.; Materials - D.T.S., İ.Ö., F.B.G., O.A.; Data collection and/or Processing - D.T.S., İ.Ö., F.B.G.; Analysis and/or Interpretation - O.A.; Literature Search - O.A.; Writing Manuscript - D.T.S., O.A.; Critical Review - M.Ş., N.E., E.E., Ö.G., O.A.

Declaration of Interests: The authors have no conflicts of interest to declare.

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