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Research Article

Evaluation of Atherosclerosis and Arterial Stiffness with Angiogenic Growth Factors in Chronic Kidney Disease Patients

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Abstract

Aim: Cardiovascular (CV) complications are the most common cause of mortality in patients with chronic kidney disease (CKD). The study aimed to determine the relationship between angiopoietin-2 (Ang-2) and vascular endothelial growth factor (VEGF) and atherosclerosis as determined by carotid artery intima-media thickness (CAT) and arterial stiffness (AS) as determined by brachial-ankle pulse wave velocity (bPWV) in pre-dialysis CKD patients.

Material and Method: The study included 126 (47.2%) male and 141 (52.8%) female pre-dialysis CKD patients. Presence of atherosclerosis was determined by CAT and presence of AS by bPWV. VEGF and Ang-2 serum levels were determined by enzyme-linked immunosorbent assays (ELISA).

Results: CAT, bPWV, and log10 Ang-2 values were significantly higher in patients compared to the healthy control group. Estimated glomerular filtration rate (eGFR), C-reactive protein (CRP), total cholesterol, triglycerides, CAT, and bPWV were higher and spot urine protein creatinine ratio was lower in patients with high mean log10 Ang-2 compared to the patients with low mean log10 Ang-2. There was a significant correlation between log10 Ang-2 and bPWV and CAT, and an inverse relationship with log10 VEGF.

Conclusion: Patients with CKD had increased development of atherosclerosis and AS, increased serum Ang-2 levels compared to healthy individuals. Ang-2 was significantly correlated with renal function and inversely correlated with proteinuria. Ang-2 was found to be correlated with inflammation and hyperlipidemia. A significant correlation was observed between Ang-2 and atherosclerosis and AS, and an inverse relationship was found with VEGF.

Keywords: Atherosclerosis, arterial stiffness, chronic kidney disease, angiopoietin-2, vascular endothelial growth factor

INTRODUCTION

The risk of death due to cardiovascular (CV) diseases is quite high in those with chronic kidney disease (CKD). An early sign of atherosclerosis is an increase in arterial intima-media thickness. Carotid artery intima-media thickness (CAT) using ultrasonography is a non-invasive, inexpensive, and easily applicable method preferred for determining the presence of atherosclerosis (1). Increased CAT is thought to be an early sign of the development of atherosclerosis in cerebral, peripheral and coronary arterial vascular beds. Increased endothelial microparticles due to increased calcium-phosphate product as a result of hyperparathyroidism in CKD patients may cause changes in the artery wall and cause atherosclerosis. Arterial stiffness (AS) is common in CKD patients A study suggested that endothelial dysfunction, advanced age, and infections are the risk factors for AS in CKD patients (2). The brachial-ankle pulse wave velocity (bPWV) device was designed to record the pulse waves of the brachial and posterior tibial arteries automatically and simultaneously using an automated oscillometric method. Determination of AS in CKD patients with the bPWV device is easy to perform, reproducible, and yields similar results to other methods known as the gold standard (3).

Angiopoietins provide vascular stabilization by binding to the endothelium-specific tyrosine kinase member receptor.

CITATION

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Angiopoietin-2 (Ang-2) is synthesized by endothelial Weibel-Palade bodies (WPB), binds to the endothelial receptor Tie-2, and plays an antagonistic role when endothelial cells are under stress. Vascular endothelial growth factors (VEGF) are effective in lymphangiogenesis, angiogenesis, and inflammation and synthesized from distal tubule and glomerular epithelial cells in the kidney. VEGF levels increase as Ang-2 increases. Ang-2 enables new vessel formation in the presence of VEGF. Ang-2 causes vascular regression and endothelial cell death in the absence of VEGF. VEGF and Ang-2 are thought to be compatible to form the microvasculature.

Matsunaga et al. suggested that vascular angiogenesis is an event that involves co-expression of both VEGF and Ang-2 (4). Lee et al. suggested that high Ang-2 and VEGF levels are associated with CV, including congestive heart failure and coronary artery disease (5). Lorbeer et al. suggested that relationship between CV mortality and Ang-2 (6). Chang et al. stated that high Ang-2 levels predict kidney failure in CKD patients (7).

Studies examining the angiogenic growth factors, atherosclerosis and AS in CKD patients are limited in number and the results are conflicting. Therefore, the present study aimed to investigate the relationship between the angiogenic growth factors Ang-2 and VEGF and atherosclerosis and AS in pre-dialysis CKD patients.

MATERIAL AND METHOD

Patient Selection

This prospective study was conducted with patients with CKD who applied to the nephrology outpatient clinic between January 2022 and January 2023.

Our study included 126 (47.2%) male and 141 (52.8%) female pre-dialysis CKD patients. The healthy control group consisted of 70 people who had no known disease or medication. Patients with no known history of pacemaker, coronary artery disease, or heart failure and over 18 years of age participated in the study. Exclusion criteria were: history of dialysis or kidney transplantation, history of active infection or malignancy within the last 3 months, previous angiographically proven coronary artery disease and therefore undergone surgical or mechanical revascularization, moderate to severe valvular insufficiency or valvular stenosis, known peripheral vascular disease, atrial fibrillation, atrial flutter, other tachyarrhythmias and bradyarrhythmias, severe left ventricular systolic dysfunction, congenital heart disease, respiratory system disease, systemic disease involving the aorta (such as Marfan, Ehler-Dahnlos). This study ethics committee numbered TABED 1-24-226 from Ankara City Hospital (date: 17/07/2024).

Clinical Measurements

Height-weight measurements, age, gender, medications, and comorbid diseases were determined. Body mass index (BMI) was calculated. Patients who had previously used antihypertensive medication or had systolic blood pressure (SBP) ≥140 mmHg and diastolic blood pressure (DBP) ≥90 mmHg were considered hypertensive. Fasting blood sugar ≥126 mg/dL and/or use of insulin or antidiabetic medication was considered diabetes mellitus (DM).The estimated glomerular filtration rate (eGFR) was calculated according to the formula by Levey et al. (8).

Laboratory Measurements

Serum creatinine, C- reactive protein (CRP), total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglyceride and low-density lipoprotein (LDL) levels were determined. Morning urine is preferred for urine laboratory testing. After the patient's urine is collected, it is sent to the laboratory. The laboratory measures the amount of protein and creatinine in the urine. Then, using these values, spot urine protein/creatinine ratio (SUPC) is calculated. VEGF and Ang-2 levels were measured using commercial enzyme-linked immunosorbent assay (ELISA) kits. Analytic range and sensitivity levels were 21-1497 pg/mL and <4 pg/mL for VEGF, 59.5-3980 pg/mL and 35.4 pg/mL for Ang-2.

Brachial-ankle pulse wave velocity

A noninvasive oscillometric aortic pressure measurement technique was used to measure pulse wave velocity (PWV) values in all patients. SphygmoCor (AtCor Medical Instruments) pulse wave analyzer was utilized as the measuring device. With the selected device, both left- and right-sided bPWV values were measured from cuffs both upper arms and ankles as previously described (9). The distances between the measurement sites of bPWV were automatically calculated according to the height of the patients. The length from the suprasternal notch to the brachial (Bb) and from the suprasternal notch to the ankle (Ba), and then the latency from the rise point of the brachial to the rise point (Bba) of each ankle waveform, were calculated. BPWV value was measured with the formula (Ba-Bb)/Bba.

Carotid artery intima-media thickness

Carotid artery intima-media thickness values were first measured in both internal carotid arteries with an ultrasonography device (Logiq P5 and linear probe). Three measurements were taken and the mean CAT was calculated as the average of the total measurements from both carotid arteries. In ultrasound B mode examination, the site between the echogenicity of the vascular cavity and the echogenicity of the media/adventitia layer of the vessel was visualized and measurements were taken from this site (10).

Statistical Analysis

IBM SPSS software was used in data analysis. Conformity to normal distribution was evaluated with the Kolmogorov-Smirnov test. Pearson chi-square test was

used to examine gender. Evaluation of laboratory data was made with the Mann Whitney U test, demographic finding, CAT and bPWV values. The correlation between log10 Ang-2 and log10 VEGF data, which do not show a normal distribution, and laboratory, CAT and bPWV data were analyzed with the Spearman rho correlation coefficient. Factors associated with Log10 Ang-2 and log10 VEGF were determined by logistic regression model. Frequency (percentage) was used for categorical data, and mean±standard deviation was used for quantitative data. The statistical significance level was determined as 0.05.

RESULTS

Patients' Characteristics

267 predialysis CKD patients were included. The average age of patients was 52.51±7.44 years.126 (47.2%) were male and 141 (52.8%) were female. A healthy control group of 70 people was created. Mean CAT was 0.67±0.16 mm, and bPWV was 8.79±1.87 m/sec. BMI (p=0.021), SBP, SUPC, CRP, total cholesterol, CAT, bPWV (all p<0.001), triglycerides (p=0.010), LDL-C (p=0.013), log10 Ang-2 (p=0.028) were higher in patients compared to healthy participants (Table 1).

Table 1. Clinical, demographic and laboratory values of the patient and healthy control group

	Patients (n=267) Mean±S.D./n (%)	Healthy control group (n=70) Mean±S.D./n (%)	p
Age (years)	53.94±11.11	52.51±7.44	0.226*
Male/female	126 (47.2)/141 (52.8)	28 (40)/42 (60)	0.282**
BMI (kg/m²)	28.31±4.07	26.87±4.07	**0.021***
Hypertensive nephrosclerosis	252 (94.4)		
Diabetic nephropathy	43 (16.1)		
SBP (mmHg)	135.32±22.83	118.67±11.02	**<0.001***
ACEinh/ARB	31 (11.6)/109 (40.8)		
Calcium channel blockers	119 (44.6)		
Beta blockers	62 (23.2)		
Alpha blockers	10 (3.7)		
Diuretics	36 (13.5)		
Others	29 (10.9)		
Vitamin D/vitamin D analogue use	59 (22.1)		
Use of oral phosphate binder	2 (0.7)		
Stage 3 CKD	149 (55.8)		
Stage 4 CKD	93 (34.8)		
Pre-dialysis stage 5 CKD	25 (9.3)		
eGFR (mL/min/1.73 m²)	29.94±16.4	90.71±6.03	**<0.001***
SUPC (g/day)	646.31±597.43	52.33±62.96	**<0.001***
CRP (mg/dL)	4.4±3.55	2.43±2.68	**<0.001***
Total cholesterol (mg/dL)	198.79±36.26	147.43±41.63	**<0.001***
Triglyceride (mg/dL)	158±107.83	144.88±46.05	**0.010***
LDL-C (mg/dL)	122.51±34.38	107.09±39.07	**0.013***
HDL-C (mg/dL)	48.47±14.19	62.79±31.96	**<0.001***
Log10 Ang-2 (pg/mL)	3.26±0.06	3.26±0.11	**<0.028***
Log10 VEGF (pg/mL)	2.29±0.21	2.25±0.2	0.317*
CAT (mm)	0.67±0.16	0.6±0.55	**<0.001***
bPWV (m/sec)	8.79±1.87	6.58±0.96	**<0.001***

Data are presented as n (%), mean±SD; * Mann Whitney U test, **Pearson chi-square test; Abbreviations: BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, ACEinh: angiotensin converting enzyme inhibitor, ARB: angiotensin II receptor blocker, eGFR: estimated glomerular filtration rate, SUPC: spot urine protein creatinine ratio, CRP: C reactive protein, LDL-C: low density lipoprotein cholesterol, HDL-C: high density lipoprotein cholesterol, Ang-2: angiopoietin 2, VEGF: vascular endothelial growth factor, CAT: carotid artery intima-media thickness, bPWV: Brachial-ankle pulse wave velocity

Patient characteristics according to median angiogenic growth factor levels

The median log10 Ang-2 value was 3.26. eGFR, total cholesterol, bPWV (all p=0.001), CRP (p=0.003), triglycerides (p=0.020), LDL-C (p<0.001) and CAT (p=0.004) were significantly higher and SUPC (p<0.001) was significantly lower in patients with log10 Ang-2>3.26 compared to those with log10 Ang-2≤3.26 (Table 2). The median log10 VEGF value was 2.3 pg/mL. SUPC (p<0.001) was significantly higher and eGFR, CRP, triglycerides, LDL-C, CAT, and bPWV (all p<0.001) were lower in patients with log10 VEGF>2.3 compared to those with log10 VEGF≤2.3 (Table 3).

Table 2. Patient characteristics according to median log10 Ang-2 levels

	Log10 Ang-2 (pg/mL)≤3.26 (n=107)	Log10 Ang-2 (pg/mL)>3.26 (n=160)	p
eGFR (mL/min/1.73 m²)	22.35±10.91	33.34±19.44	**0.001**
SUPC (g/day)	1026.52±692.93	431.55±348.82	**<0.001**
CRP (mg/dL)	3.35±1.8	6.07±4.37	**0.003**
Total cholesteroL (mg/dl)	186.02±38.63	210.49±33.27	**0.001**
Triglyceride (mg/dL)	125.98±33.52	145.53±39.47	**0.020**
LDL-C (mg/dL)	127.76±23.97	80.5±43.34	**<0.001**
CAT (mm)	0.62±0.1	0.69±0.21	**0.004**
bPWV (m/sec)	8.16±1.45	9.96±1.63	**<0.001**

Data are presented as n (%), mean±SD, Mann Whitney U test

Table 3. Comparison of patient characteristics according to median log10 VEGF levels

	Log10 VEGF (pg/mL) (n=102)	Log10 VEGF (pg/mL)>2.3 (n=165)	p
eGFR (mL/min/1.73 m²)	37.65±17.07	20.61±12.4	**<0.001**
SUPC (g/day)	500.1±747.89	877.77±410.53	**<0.001**
CRP (mg/dL)	6.12±4.14	3.16±2.05	**<0.001**
Total cholesterol (mg/dl)	201.52±49.46	197.08±24.89	**<0.001**
Triglyceride (mg/dL)	136.38±41.05	116.42±34.05	**<0.001**
LDL-C (mg/dL)	122.01±41.19	92.57±37.32	**<0.001**
CAT (mm)	0.75±0.07	0.58±0.18	**<0.001**
bPWV (m/sec)	9.42±2.11	8.75±1.19	**<0.001**

Data are presented as n (%), mean±SD, Mann Whitney U test

Markers correlated with angiogenic growth factors

Log10 Ang-2 was significantly positively CAT (r=0.373, p<0.001) (Figure 1), and bPWV (r=0.274, p<0.001) (Figure 2). A significant positive correlation was between log10 VEGF and SUPC (r=0.134, p=0.043) and an inverse correlation between log10 VEGF and CAT (r=-0.555, p<0.001) (Figure 3), (Table 4).

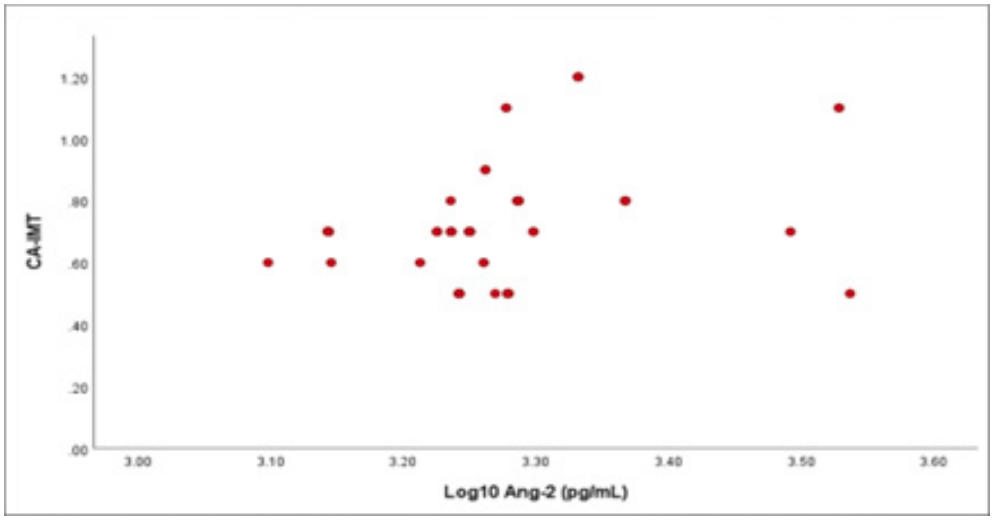

Figure 1. Relationship with log10 Ang-2 and CAT

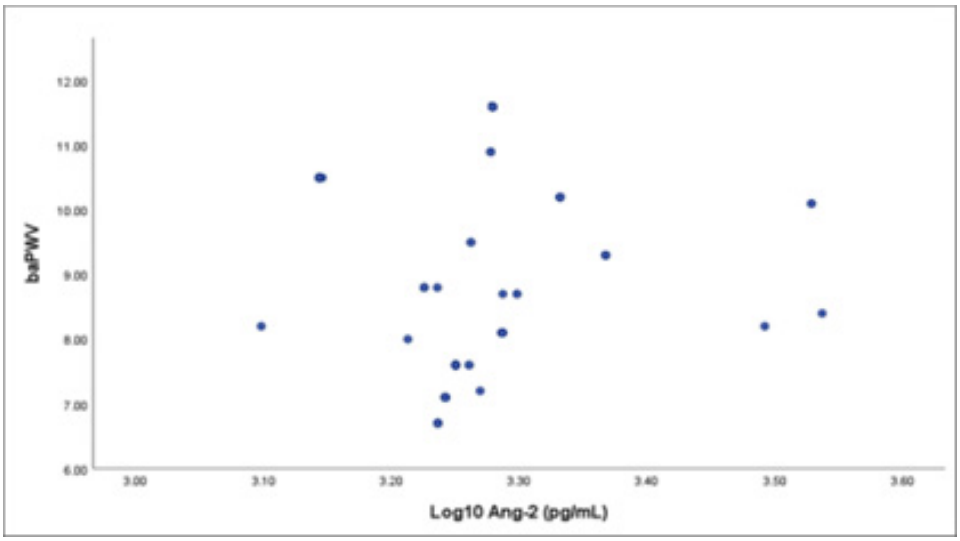

Figure 2. Relationship with log10 Ang-2 and bPWV

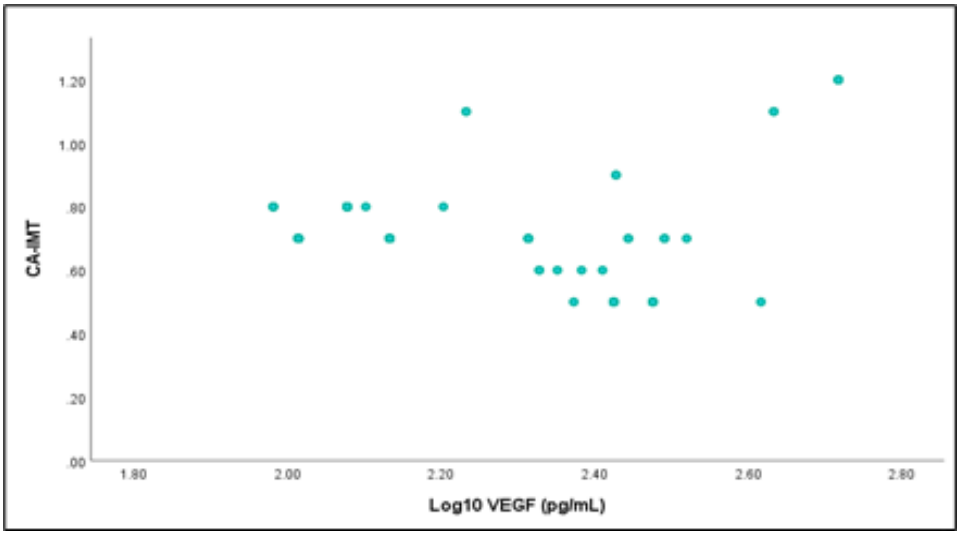

Figure 3. Relationship with log10 VEGF and CAT

Table 4. Factors associated with angiogenic growth factors in correlation analysis

	Log10 Ang-2 (pg/mL)		Log10 VEGF (pg/mL)	
	r	p	r	p
eGFR (mL/min/1.73 m²)	0.317	**<0.001**	-0.586	**<0.001**
SUPC (g/day)	-0.706	**<0.001**	0.134	**0.043**
CRP (mg/dL)	0.038	**<0.001**	-0.585	**<0.001**
Total cholesterol (mg/dl)	0.496	**<0.001**	-0.042	0.528
Triglyceride (mg/dL)	0.202	**0.002**	-0.238	**<0.001**
LDL-C (mg/dL)	0.695	**<0.001**	-0.083	0.212
CAT (mm)	0.373	**<0.001**	-0.555	**<0.001**
bPWV (m/sec)	0.274	**<0.001**	-0.554	**<0.001**

r: Spearman's rho correlation coefficient

In univariate logistic regression analysis, an increase in log10 Ang-2 (pg/mL) level was detected as the patients' eGFR value increased (OR=1.014, 95%CI 1.006–1.023).

In the model obtained by multivariate logistic regression analysis with the forward stepwise Wald method, a 1.073-fold increase in the log10 Ang-2 (pg/mL) level was detected with the increase in the eGFR value of the patients (OR=1.073, 95%CI 1.031–1.118). An increase in log10 Ang-2 (pg/mL) level was detected as the bPWV value of the patients increased (OR=1.673, 95%CI 1.131–2.476).

With the model created as a result of multivariate analysis, 81.2% of the cases were classified correctly.

In univariate logistic regression analysis, a 0.099-fold decrease in log10 VEGF (pg/mL). As the bPWV value of the patients increased, a 1.031-fold decrease was detected in log10 VEGF (pg/mL) levels (OR=1.031, 95%CI 1.003–1.061).

The increase in the bPWV value of the patients, a 0.386-fold decrease in the log10 VEGF (pg/mL) level was detected (OR=0.386, 95%CI 0.211–0.708) (Table 5). With the model created as a result of multivariate analysis, 96.5% of the cases are classified correctly.

Table 5. Factors associated with angiogenic growth factors in multivariate analysis

	Univariate (Log10 Ang-2)		Multivariatefwald (Log10 Ang-2)		Univariate (Log10 VEGF)		Multivariatefwald (Log10 VEGF)	
	OR (95% GA)	p	OR (95% GA)	p	OR (95% GA)	p	OR (95% GA)	p
eGFR (mL/min/1.73 m²)	1.014 (1.006-1.023)	**0.001**	1.073 (1.031-1.118)	**0.001**	0.99 (0.982-0.998)	**0.015**		
SUPC (g/day)	0.999 (0.999-1)	**<0.001**	0.995 (0.993-0.997)	**<0.001**	1.001 (1-1.001)	**<0.001**		
CRP (mg/dL)	1.103 (1.052-1.156)	**<0.001**	1.482 (1.168-1.88)	**0.001**	1.127 (1.073-1.184)	**<0.001**	3.674 (2.198-6.141)	**<0.001**
Total cholesterol (mg/dl)	1.001 (1-1.003)	0.060				1.001 (1-1.002)	0.147	
Triglyceride (mg/dL)	1.002 (1-1.004)	**0.047**				1.001 (1-1.003)	0.113	
LDL-C (mg/dL)	1.005 (1.002-1.007)	**<0.001**	0.953 (0.934-0.973)	**<0.001**	1 (0.997-1.002)	0.689	0.705 (0.626-0.794)	**<0.001**
CAT (mm)	1.396 (0.95-2.052)	0.089			0.936 (0.639-1.371)	0.733	0 (0-0.005)	0.051
bPWV (m/sec)	1.036 (1.007-1.065)	**0.016**	1.673 (1.131-2.476)	**0.010**	1.031 (1.003-1.061)	**0.032**	0.386 (0.211-0.708)	**0.002**

OR: Odds ratio, CI: confidance interval, fwald: Forward Wald Method, Accuracy=0.978

DISCUSSION

We observed that the progression of atherosclerosis and AS was increased in pre-dialysis chronic kidney patients compared to the healthy participants. Ang-2 was significantly correlated with renal function and inversely correlated with proteinuria. Ang-2 was significantly correlated with CRP and hyperlipidemia. A significant correlation was observed between Ang-2 and atherosclerosis and AS, and an inverse correlation was studied between VEGF and AS and atherosclerosis.

Hara et al. demonstrated that an imbalance between angiogenesis-related factors plays a role in the progression of CKD in their experimental study (11). Agyekum et al. reported that increased serum Ang-2 levels were observed in diabetics. In contrast to other studies, they argued that there was no difference in VEGF levels between diabetics and non-diabetics, and this might be attributed to the ethnic diversity in the comparative study including Caucasians and people of African origin (12). Nadar et al. Suggested that Ang-2 and VEGF levels increase in hypertensive CKD patients compared to normotensive individuals in the ASCOT study (13). Futrakul et al. suggested that decreased circulating VEGF levels and increased Ang-2 levels were observed in CKD patients with moderate to advanced renal dysfunction (14). In a study suggested that Ang-2 serum values increased in 61 hemodialysis and 24 peritoneal dialysis patients compared to the healthy participants. They suggested that the increased Ang-2 levels might be attributed to increased WPB exocytosis in CKD patients related to decreased nitric oxide levels (15). In another study, It was reported that an increase in serum levels was observed due to a decrease in renal excretion of Ang-2 and an increase in its impaired synthesis from the kidneys (16). In our study, serum Ang-2 levels were found to be increased in CKD patients compared to healthy control group. This may be due to excessive WPB exocytosis in CKD patients in the presence of physical damage, endogenous chemicals, high dimethylarginine, as reported by Fiedler et al. (17). There was no difference in VEGF levels between patients and healthy control group. Tsai et al. Suggested that significant relationship between Ang-2 and renal progression in non-dialyzed CKD patients (18).

Lee et al. reported that high circulating levels of Ang-2 are correlated with CV diseases, including congestive heart failure and coronary artery disease (5). Chong et al. suggested that the relationship between elevated serum Ang-2 levels and increased CV events was more pronounced than Angiopoietin-1 (19). Molnar et al. reported that circulating Ang-2 predicted mortality in renal transplant recipients (20). In another study suggested that high level serum Ang-2 values were significantly correlated with major adverse CV events (21). This show us angiogenic growth

factors are associated with increased CV events. Therefore, we examined the corelation between VEGF and Ang-2 and atherosclerosis and AS in patients with pre-dialysis CKD.

Atherosclerotic plaques are present in up to 30% of CKD patients. In a study reported that CAT level was an indicator of the presence of atherosclerosis (22). Mayer et al. suggested that levels of angiogenic growth factors increase with increasing CKD stage and are associated with atherosclerosis (23). David et al. suggested that Ang-2 causes atherosclerosis through vascular microinflammation and endothelial activation in pre-dialysis stage 5 CKD patients (16). In our study, we identified a correlation between increased Ang-2 and atherosclerosis determined by CAT in CKD patients. An inverse correlation was observed between VEGF and atherosclerosis.

In addition to angiogenesis, Ang-2 is an important regulator in many pathophysiological processes including inflammation (24). Ang-2 is correlated with the proinflammatory response via P-selectin, E-selectin, and vascular cell adhesion molecule 1 (16). High Ang-2 serum levels can trigger the inflammatory gene expression and stimulates the endothelium to the inflammatory response. Circulating Ang-2 in patients with CKD was shown to be correlated with markers of systemic microinflammation (5). In our study, a significant correlation was observed between Ang-2 and CRP, which is considered as a marker of inflammation.

Upadhyay et al. reported increased AS development from early-stage renal failure (25). Morimoto et al. observed that AS progress increased as the stage of renal failure progressed in CKD patients (26). In our study, increased AS development was determined in pre-dialysis CKD patients compared to control group.

David et al. reported that increased Ang-2 levels were observed in 43 stage 4 pre-dialysis and 85 stage 5 dialysis (peritoneal dialysis, hemodialysis) patients. It was suggested that this difference could be attributed to the fact that the Ang/Tie axis causes different effects on coronary artery endothelium and peripheral artery endothelium. They reported that Ang-2 can be used as an indicator of mortality in stage 4-5 CKD patients independently of AS. The authors suggested that no relationship exists between Ang-2 and AS, which might be attributed to the fact that other factors play a role in patients undergoing dialysis that are different from those in pre-dialysis patients and that these factors may reduce the effect of Ang-2 on AS (27). Agyekum et al. reported increased AS development in diabetics and that it was correlated with increased Ang-2 (12). In our study, a relationship was found between Ang-2 and AS in pre-dialysis CKD patients. This could be due to the involvement of vascular smooth muscle cell transformation and local inflammation in the pathogenesis of AS as reported by Chang et al. (28).

CONCLUSION

We determined increased atherosclerosis , AS and serum Ang-2 levels were determined in pre-dialysis CKD patients compared to healthy individuals. Those with higher Ang-2 levels had higher renal function tests and less proteinuria. Those with higher VEGF levels had lower renal function tests and more proteinuria. Inflammation and hyperlipidemia were higher in high Ang-2 levels and lower in high VEGF levels. Atherosclerosis development was higher in high Ang-2 levels and lower in high VEGF levels. Ang-2 was significantly correlated with atherosclerosis and AS, whereas VEGF was inversely correlated. High Ang-2 serum grades in pre-dialysis CKD patients could be used as an indicator for development of adverse CV diseases. Further studies are needed to use VEGF and Ang-2 in clinical practice.

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Ethical approval: *This study ethics committee numbered TABED 1-24-226 from Ankara City Hospital (date: 17/07/2024).*

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