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Original Article

Evaluation of the Association of Serum Sclerostin and Carotid Intima Media Thickness with Chronic Kidney Failure and Kidney Transplantation

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SUMMARY

Purpose: This study aimed to determine the serum sclerostin levels in kidney transplant recipients, dialysis patients, and patients with non-dialysis chronic kidney disease (CKD), and evaluate their associations with carotid intima-media thickness (CIMT) and carotid artery plaque presence.
Methods: The study groups included kidney transplant recipients (n = 61), dialysis patients (n = 43), non-dialysis CKD patients (n = 43), and healthy controls (n = 19). Serum sclerostin levels were measured by the ELISA method. All participants underwent imaging tests for the evaluations of CIMT and carotid plaque presence.
Results: Serum sclerostin levels were highest in dialysis patients, followed by the non-dialysis CKD group. Kidney transplant patients and healthy controls had the lowest sclerostin levels. There was a positive correlation between CIMT and sclerostin levels in the CKD group. Sclerostin levels were significantly high in individuals with calcified plaques.
Conclusion: The CIMT and serum sclerostin levels of kidney transplant recipients compared to those of CKD patients with and without dialysis may suggest that transplantation may prevent further atherosclerosis, with sclerostin levels promising a predictive role.

1. Introduction

In patients with chronic kidney disease (CKD), cardiovascular disease (CVD) is a major comorbidity.[1] Ongoing inflammation plays a role in the pathogenesis of CVD in patients with CKD.[2] This risk continues in end-stage kidney disease (ESRD) patients, who underwent kidney transplantation.[3] A study conducted by Hornum et al.[4] reported findings concerning arterial functions, arterial pressure, and improvement of endothelial dysfunction in kidney transplant recipients. Other studies reported findings showing that atherosclerosis and coronary artery calcification continued and transplantation did not reverse the atherosclerotic process in this population.[5] Unconventional risk factors indicating oxidative stress are considered substantial for the CVD risk in uremic patients.[6] In kidney transplant patients without a diagnosis of CVD; ongoing atherosclerosis, inflammation, and oxidative stress were found, but a specific rate of improvement was reported compared to hemodialysis and peritoneal dialysis patients.[7]

Sclerostin increases vascular smooth muscle calcification *in vitro*.[8] Consistently, an increase in serum sclerostin levels, independent of inflammation and age, was associated with cardiovascular mortality in CKD.[9] However, in the literature, the data about the improvement of serum sclerostin levels in kidney transplant recipients are scant. Carotid intima-media thickness (CIMT) is a reliable marker of atherosclerosis and is frequently used as a parameter in clinical studies[10] and three-dimensional carotid artery imaging by ultrasonography is more sensitive and reproducible than unidimensional evaluations.[11]

In the present study, we aimed to determine the relationship between sclerostin, CIMT, and carotid plaque presence in kidney transplant recipients and CKD patients with or without dialysis, and compare these results with those of healthy individuals.

2. Material and methods

This study was planned to include CKD patients and healthy controls, making a total of 166 individuals. CKD patients were kidney transplant recipients or patients with or without dialysis. Kidney transplant recipients had undergone kidney transplantation in our hospital in the period between January 2016 and January 2017. Dialysis patients underwent routine dialysis. The study protocol was evaluated by the Clinical Research Ethics Committee and accepted with approval number 2016-546. In addition, support for the study was deemed appropriate by the Scientific Research Projects Commission with project number 161518020.

Study participants were divided into four groups as follows:

Group 1: Kidney transplant recipients. This group included patients, who had undergone kidney transplantation at least six months

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before enrollment in the study.

Group 2: Chronic kidney disease patients. This group included stage 2–5 chronic kidney disease patients with urine output. We defined CKD as kidney structure or function abnormalities present for three months and associated with health implications, and staged CKD based on glomerular filtration rate (GFR) estimated by the Modification of Diet in Kidney Disease (MDRD) formula. The CKD stage-2 group included patients with eGFR in the range between 60 and 89 ml/min/1.73 m^2. The stage-3, 4, and 5 groups included patients in the eGFR range of 30 and 59, 15 and 29, and < 15 ml/min/1.73 m^2, respectively.[12]

Group 3: Dialysis patients. This group included patients receiving hemodialysis and peritoneal dialysis treatment.

Group 4: Control group. This group included individuals, who were admitted to Meram Medical Faculty Internal Medicine outpatient clinic for various reasons and whose physical examinations and tests did not reveal any pathological finding.

The exclusion criteria were as follows: acute kidney failure at the time of blood sample collection or during the preceding 6 months, acute or chronic rejection therapy; a history of cardiovascular events, or stroke; infection, uncontrolled hypertension (office measurements of higher than 140 mmHg systolic and 90 mmHg diastolic blood pressure levels despite the use of one or more antihypertensives), malignancy, diabetes, a fasting plasma glucose level of ≥ 126 mg/dL (6.99 mmol/L), an HbA1c level of ≥ 6.5%, or a randomly measured glucose level of ≥ 200 mg/dL (11.1 mmol/L), high body mass index (BMI) (BMI > 35), an emergency medical condition (such as respiratory failure due to interstitial disease), cardiovascular disease (ischemic signs in electrocardiogram), or the use of supplements that would affect inflammation parameters (Figure 1).

2.1. Carotid intima-media thickness and the evaluation of plaque presence

For CIMT, plaque presence and, intimal calcified atheroma plaque presence all patients and healthy individuals in the study underwent measurements and evaluations performed by an experienced investigator using B-mode and Doppler sonography while subjects were lying in a supine position, with the head in extension. Carotid arteries were measured with an Applio XG ultrasonography device (Toshiba Medical Systems, Tokyo, Japan) using a 10-MHz linear probe (Model PVT-375BT, Serial number: FDA 11Y4472). Internal and external carotid arteries, the common carotid artery, and the carotid sinus were visualized on both sides. CIMT was measured at the distal part of the common carotid artery, 15–20 mm proximal to the carotid sinus. Two bright echogenic lines on the arterial wall were evaluated as intima and media. The distance between these two bright lines was measured as CIMT. The mean of three measurements on either side was calculated and recorded as the right and left CIMT. Care was exercised to measure CIMT at the thickest place. An atherosclerotic plaque was defined as a CIMT-value of > 1.2 mm.

2.2. Biochemical analysis

Venous blood samples were collected after an overnight fast and stored at -80 °C for biochemical analysis. Serum creatinine, urea, aspartate aminotransferase, alanine aminotransferase, calcium, albumin, uric acid, total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglyceride, and phosphorus (P) levels were determined by using a Synchron LX20 system (Beckman Coulter, USA) with original Beckman reagents. HDL-C levels were determined by a direct enzymatic method without precipitation. Low-density lipoprotein cholesterol levels were calculated using the Friedewald formula.[13] Using automated clinical chemistry, high-sensitivity C-reactive protein (hs-CRP) levels were measured with a sensitive immunoturbidimetric test (Diasis Diagnostic System). A reference hs-CRP value of < 10 mg/L was considered normal for adults.

2.3. Glomerular filtration rate assessment

GFR was calculated using the simplified version of MDRD study

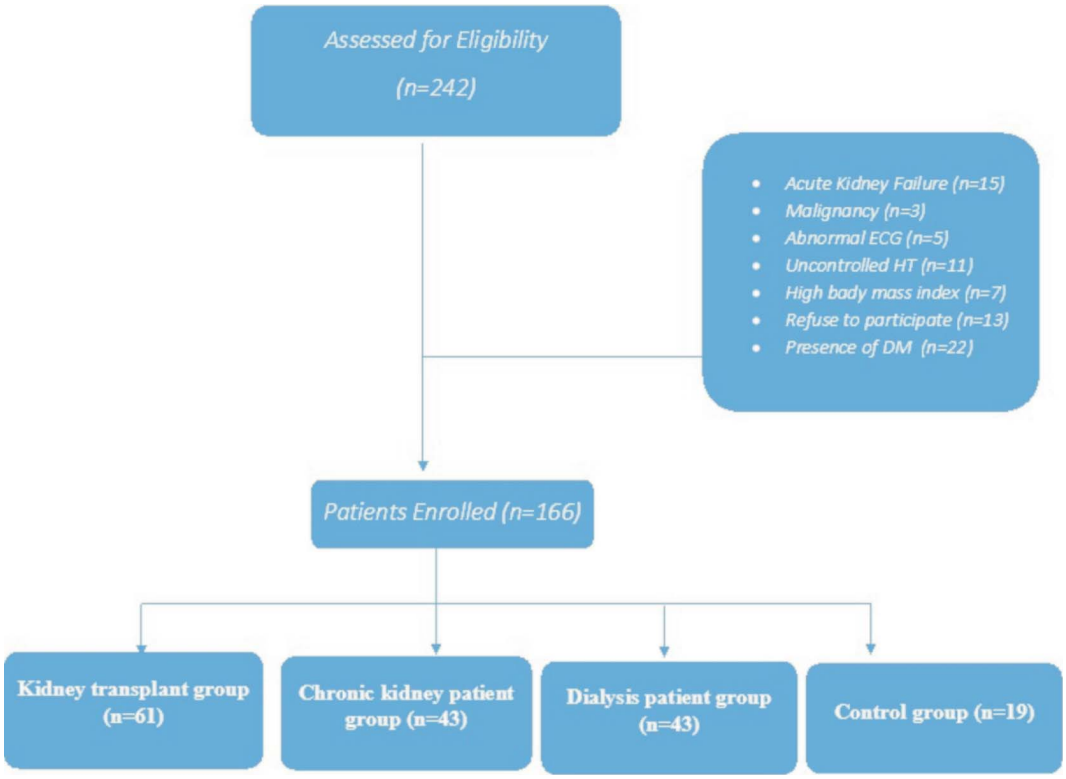

Figure 1. Flow chart.

estimation equation, GFR = 186 * Creatinine-1.154 * Age-0.203 * 1.212 (if African-American) * 0.742 (if female), as defined by Levey.[14]

2.4. Statistical method

Statistical analyzes of the study were performed by using the SPSS 15 (IBM Inc., Armonk, NY) software. Mean and standard deviation values were used for numerical data, and frequency and percentage values were used for categorical data. For numerical data comparisons between independent study groups, the Kruskal-Wallis test was used to compare more than two groups and the Mann-Whitney U test was used to compare two groups. The chi-square test was used for categorical data comparisons. Spearman's non-parametric correlation analysis was used to examine correlations. Linear regression analysis was performed to determine the independent determinants of carotid intima-media thickness. A value of 5% was defined as the type-1 error margin and the statistical significance limit.

3. Results

The study included 61 (36.7%) kidney transplant recipients (post-transplantation follow-up duration: 72 ± 12 months, mean dialysis vintage prior to transplant: 89 ± 14 months), 43 (25.9%) CKD patients (Grades 2–5), 43 (25.9%) dialysis patients (mean dialysis vintage: 85 ± 13 months), and 19 (11.4%) healthy individuals. When the general characteristics of the groups were examined, the mean age of the patients was 45.4 ± 12.2 years in the kidney transplant group, 63.9 ± 14.2 years in the CKD group, 49.2 ± 14.3 years in the dialysis group, and 40.1 ± 13.7 years in the control group. Table 1 shows the comparison of age, serum sclerostin levels, CIMT, and plaque presence between the study groups.

Post-hoc analyzes revealed differences in age, serum sclerostin levels, and CIMT between the groups (Figure 2). Age was higher in the CKD group compared to the kidney transplant and dialysis patients and healthy controls, and similar in the latter three groups. Se-

Table 1
Comparison of clinical characteristics between study groups.

	Kidney transplant (n = 61) mean ± SD	Dialysis (n = 43) mean ± SD	CKD (n = 43) mean ± SD	Control (n = 19) mean ± SD	p
Age (years)	45.4 ± 12.2	49.2 ± 14.3	63.9 ± 14.2	40.1 ± 13.7	**< 0.001**
Serum sclerostin (pg/mL)	134.6 ± 56.3	269.6 ± 161.5	188 ± 92.7	126 ± 59.7	**< 0.001**
Carotid intima-media thickness (mm)					
Right	0.68 ± 0.12	0.72 ± 0.16	0.78 ± 0.14	0.6 ± 0.08	**< 0.001**
Left	0.7 ± 0.15	0.72 ± 0.16	0.78 ± 0.2	0.61 ± 0.09	**0.014**
	n (%)	n (%)	n (%)	n (%)	
Plaque in the carotid artery					
Right					0.089
No plaque	51 (83.6)	32 (76.2)	16 (61.5)	13 (100)	
There is plaque, not calcified	1 (1.6)	1 (2.4)	1 (3.8)	-	
There is plaque, calcified	9 (14.8)	9 (21.4)	9 (34.6)	-	
Left					0.081
No plaque	50 (82)	30 (71.4)	17 (65.4)	13 (100)	
There is plaque, not calcified	1 (1.6)	1 (2.4)	3 (11.5)	-	
There is plaque, calcified	10 (16.4)	11 (26.2)	6 (23.1)	-	

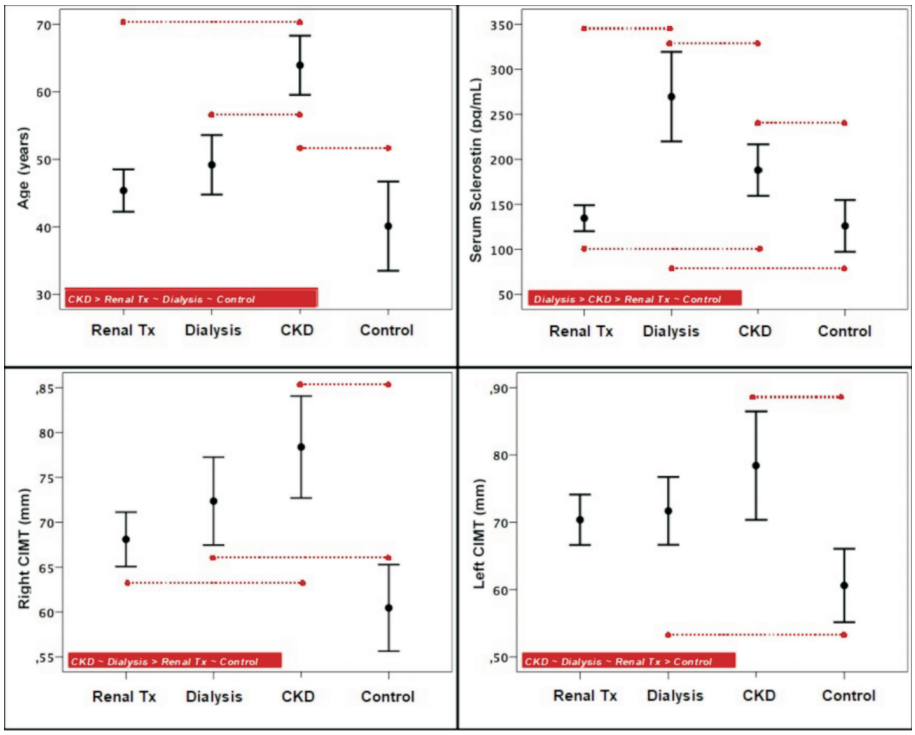

Figure 2. Post hoc analyses of clinical features among study groups.

rum sclerostin values were the highest in dialysis patients, followed by CKD patients, and the lowest in kidney transplant patients and healthy controls with similar values. Right CIMT was similar in the CKD and dialysis groups but these values were higher than those found in the kidney transplant and control groups. In the two latter groups, CIMT values were similar. Left CIMT values were similar across the CKD, dialysis, and kidney transplant groups but higher than the values found in the control group. Of these variables, age ($p < 0.001$), serum sclerostin levels ($p < 0.001$), right CIMT ($p < 0.001$), and left CIMT ($p = 0.014$) were statistically significantly different but plaque presence in the right carotid artery ($p = 0.089$) and left carotid artery ($p = 0.081$) did not show a significant difference across the groups (Table 1).

When the relationship between serum sclerostin levels and right CIMT was evaluated, there was not a significant difference between these two parameters in the kidney transplant group ($r = 0.082$; $p = 0.529$), dialysis group ($r = 0.180$; $p = 0.254$), and control group ($r = 0.213$; $p = 0.485$). However, there was a moderately strong and statistically significant positive relationship in the CKD group ($r = 0.451$; $p = 0.021$). There were no significant relationships between serum sclerostin levels and left CIMT in the kidney transplant ($r = 0.159$; $p = 0.220$) and dialysis ($r = 0.063$; $p = 0.691$) groups, but there was a moderately strong and statistically significant positive relationship in the CKD group ($r = 0.396$; $p = 0.045$) (Table 2).

In the kidney transplant group, serum sclerostin values did not show a statistically significant relationship with either right ($p = 0.075$) or left ($p = 0.077$) carotid artery plaque presences. Similarly, serum sclerostin values in the dialysis group did not show a statistically significant relationship with either right ($p = 0.972$) or left ($p = 0.738$) carotid artery plaque presences. In the CKD group, serum sclerostin values were statistically significantly higher in the presence of calcified plaques on both the right ($p = 0.037$) and left ($p = 0.009$) sides.

When biochemical parameters were compared between study groups; hemoglobin ($p < 0.001$), neutrophil/lymphocyte ratio (NLR) ($p = 0.013$), parathormone ($p = 0.001$), calcium ($p = 0.003$), phosphorus ($p < 0.001$), urea ($p < 0.001$), creatinine ($p < 0.001$), and eGFR ($p < 0.001$) values were significantly different between the groups (Table 3).

According to the results of the multivariate linear regression analysis performed to determine the independent determinants of CIMT; NLR and age in the kidney transplant group, sclerostin and duration in the dialysis group, and age in the CKD group were the independent predictors of CIMT. When the patient groups were evaluated together, sclerostin and age were the independent predictive parameters for CIMT, with statistical significance (Table 4).

Table 2
The relationship of sclerostin levels with age and CIMT in patients with kidney transplantation dialysis and CKD.

	Age (years)		Right CIMT		Left CIMT	
	r	p	r	p	r	p
Sclerostin						
Kidney transplant	**0.334**	**0.009**	0.082	0.529	0.159	0.22
Dialysis	0.249	0.107	0.18	0.254	0.063	0.691
CKD	**0.358**	**0.018**	**0.451**	**0.021**	**0.396**	**0.045**

4. Discussion

There are several major findings of the present study. Firstly, while sclerostin levels and CIMT were the highest in the hemodialysis group, they reached normal levels in the kidney transplant group, with values similar to those found in the control group. Secondly, CIMT and carotid plaque presence were positively correlated with sclerostin levels in CKD patients. Thirdly, age and sclerostin levels were independent predictors of CIMT in all groups. Finally, we determined that kidney transplantation could slow down atherosclerosis and sclerostin may serve as a marker of atherosclerosis in this population.

Sclerostin is expressed in aortic vascular smooth muscle cells and is upregulated during the arteriosclerotic calcification process.[15] Kırkpantur et al.[8] examined the relationship between circulating sclerostin levels and carotid artery atherosclerosis in hemodialysis patients and reported significantly increased sclerostin levels in patients with atherosclerotic plaques. Our study findings support this information because we found that serum sclerostin levels were significantly high in the presence of calcified plaques in the bilateral carotid arteries, especially in patients with CKD, and that CIMT and sclerostin levels were correlated.

Sclerostin is a product of the SOST gene. SOST expression was associated with bone formation as well as vascular calcification. However, whether SOST is a positive or negative inhibitor or a biomarker for vascular calcification is unclear. In 2015, Qureshi et al. analyzed 89 kidney transplant recipients and ESRD patients by comparing epigastric and coronary artery calcification and serum SOST levels. They found a positive correlation between medial vascular calcification and SOST levels but stated that the potential of SOST as a biomarker is limited.[16] Kalousova et al. reported that SOST levels increased three times in hemodialysis patients compared to the control group and were positively correlated with cardiovascular mortality. They hypothesized that SOST increased as a biomarker, not as a defense mechanism resulting from vascular calcification.[17] In a similar study, Moghazy et al. found that the SOST level was high in dialysis patients in correlation with heart valve calcification and

Table 3
Evaluation of biochemical measurements among patient groups.

	Kidney transplant (n = 61) mean ± SD	Dialysis (n = 43) mean ± SD	CKD (n = 43) mean ± SD	Control (n = 19) mean ± SD	p
hs-CRP (mg/L)	8.43 ± 11.68	15.56 ± 23.11	15.71 ± 33.74	3.43 ± 3.06	0.102
Hemoglobin (g/dl)	13.62 ± 2.15	12.52 ± 1.77	12.32 ± 1.93	14.49 ± 1.46	**< 0.001**
Neutrophil (×103/μl)	5.64 ± 1.92	5.8 ± 2.49	5.01 ± 1.9	4.48 ± 1.06	0.109
Lymphocyte (×103/μl)	1.91 ± 0.75	1.88 ± 1.24	1.8 ± 0.65	2.2 ± 0.33	0.083
NLR	3.46 ± 2.09	5.06 ± 10.12	3.16 ± 2.16	2.09 ± 0.59	**0.013**
Parathormone (pg/ml)	155.83 ± 102.33	305.83 ± 285.86	147.98 ± 150.06	67.85 ± 25.81	**0.001**
Calcium (mg/dl)	9.62 ± 0.59	9.18 ± 0.87	9.26 ± 0.62	9.62 ± 0.4	**0.003**
Phosphorus (mg/dl)	3.2 ± 0.72	4.14 ± 1.06	3.86 ± 0.99	3.65 ± 0.47	**< 0.001**
Urea (mg/dl)	50.34 ± 26.6	99.63 ± 35.03	81.66 ± 43.3	28.75 ± 7.41	**< 0.001**
Creatinine (mg/dl)	1.43 ± 0.88	7.32 ± 2.37	2.38 ± 1.84	0.86 ± 0.2	**< 0.001**
eGFR (ml/min/1.73 m^2)	69.5 ± 29.45	NA	38.05 ± 21.83	103.23 ± 18.79	**< 0.001**

Table 4
Table of CIMT independent determinants.

Group	Model	Parameters	CIMT	
			Beta	p
Kidney transplant	1	Constant		0.075
		NLR	0.575	0.001
		hs-CRP (mg/L)	-0.081	0.592
		Phosphorus (mg/dl)	-0.101	0.591
		Serum sclerostin (pg/ml)	-0.078	0.668
		Parathormone (pg/ml)	-0.153	0.323
		eGFR (ml/min/1.73 m^2)	0.017	0.93
		Age (year)	0.449	0.013
	6	Constant		< 0.001
		NLR	0.521	< 0.001
		Age (year)	0.34	0.013
Dialysis	1	Constant		0.122
		NLR	0.205	0.235
		hs-CRP (mg/L)	0.007	0.971
		Phosphorus (mg/dl)	0.205	0.21
		Serum sclerostin (pg/ml)	0.496	0.005
		Parathormone (pg/ml)	-0.159	0.331
		Age (year)	0.226	0.162
	6	Constant		< 0.001
		Serum sclerostin (pg/ml)	0.467	0.003
		Age (year)	0.279	0.065
CKD	1	Constant		0.002
		NLR	0.043	0.862
		hs-CRP (mg/L)	0.098	0.674
		Phosphorus (mg/dl)	-0.111	0.745
		Parathormone (pg/ml)	-0.154	0.675
		eGFR (ml/min/1.73 m^2)	-0.383	0.144
		Age (year)	0.272	0.318
	7	Constant		< 0.001
		Age (year)	0.433	0.031
All Groups (control group not including)	1	Constant		< 0.001
		NLR	0.112	0.221
		hs-CRP (mg/L)	0.046	0.626
		Phosphorus (mg/dl)	0.075	0.472
		Serum sclerostin (pg/ml)	0.277	0.008
		Parathormon (pg/ml)	-0.09	0.382
		eGFR (ml/min/1.73 m^2)	0.114	0.337
		Age (year)	0.375	< 0.001
	6	Constant		< 0.001
		Serum sclerostin (pg/ml)	0.24	0.008
		Age (year)	0.41	< 0.001

acted as a sensitive biomarker for valvular and vascular calcification.[18] In a study on hemodialysis patients, Jiping He et al. compared the levels of sclerostin and single-stranded miRNA 29b, which was reported to take part in cardiovascular disease and diabetes. They found a negative correlation between the levels of sclerostin and miRNA 29b and reported phosphorus, CRP, sclerostin, and miRNA 29b as independent risk factors for the presence of coronary artery calcification based on results from a multivariate logistic regression analysis.[19] In our study, sclerostin levels and CIMT were positively correlated. Taken together with the results from the abovementioned studies, it is not unreasonable to consider that sclerostin can serve as a biomarker.

Studies, which evaluated the potential factors that may be involved in decreased sclerostin levels in transplant patients, found that patient age, time elapsed after transplantation, phosphate and magnesium levels, pre-transplantation sclerostin levels, and vitamin D treatment were positively correlated with sclerostin levels measured after transplantation. However, BMI and parathormone levels were negatively correlated.[20] Pelletier et al.,[21] Mödder et al., and Amrein et al.[22,23] showed the correlation of serum sclerostin levels with patient age. Our study findings showed a positive correlation between serum sclerostin levels and age in kidney transplant recipients, CKD patients, and healthy controls, but this correlation did not occur in dialysis patients.

Studies in the literature have reported the clinical significance of the high neutrophil-lymphocyte ratio as a component of the inflammatory and immune processes occurring in CKD.[24] The higher neutrophil-lymphocyte ratio in our patient group compared to that of the control group is compatible with the findings reported in the literature.[25] Furthermore, in the multivariate linear regression analysis model, we found that the neutrophil-lymphocyte ratio was an independent predictor of CIMT in kidney transplant patients. Considering the relationship between the neutrophil-lymphocyte ratio and cardiovascular complications in chronic inflammatory processes and CKD,[26] this result is compatible with the literature.

Our study had three main limitations. First this was across-sectional analysis focusing on the relationship between sclerostin and kidney diseases. Second, our study was that our sample size was not sufficient. Therefore, less than 10 samples per variable were used in our regression analysis. Traditional and related factors were also taken in the regression analysis, so we could not reach this rate in every analysis. Third all of the patient enrolled in the study were Turkish. One should consider that our results cannot therefore be applied to all patients because of the differences between nationalities.

In conclusion, in the multivariate linear regression analyses performed to determine the independent predictors of CIMT in our study, we have found that the neutrophil-lymphocyte ratio and age in kidney transplant recipients, serum sclerostin values and age in dialysis patients, and age in CKD patients are independent predictors for CIMT. When all patients are evaluated together, serum sclerostin values and age are independent markers for CIMT.

Conflicts of interest

We declare that there are no conflicts of interest relevant to this study.

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