Study of serum sclerostin levels and its role in vascular calcification in patients with chronic kidney disease

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Objective
The aim of this work was to study serum sclerostin levels in patients with chronic kidney disease (CKD) not on dialysis and those on regular hemodialysis and its role in vascular calcification.

Background
CKD, whether starting hemodialysis (HD) or not, is associated with an increase in the risk for vascular calcification, which can only be partially explained by known classical risk factors. Sclerostin is an osteocyte-derived inhibitor of the Wnt pathway and has been shown to play a key role in vascular calcification in patients with CKD.

Patients and methods
This cross-sectional study was carried out on 80 patients with CKD attending Menoufia University Hospital. Patients were classified into 40 patients with CKD who were not on HD (group I) and 40 patients with CKD on regular HD more than 6 months (group II), who were compared with 15 controls (group III). Abdominal aortic calcification (AAC) was assessed using lateral lumbar radiography. Echocardiography was used to assess aortic valve calcification (AVC) calcification. Patient's basic clinical and biochemical data were recorded. Serum sclerostin level was measured using commercially available enzyme-linked immunosorbent assay kits.

Results
Sclerostin levels among the patients with CKD on HD (116.8±0.103.69 Pmol/l) was significantly higher than that of CKD predialysis group (28.63±0.36.26 Pmol/l), which in turn was statistically higher than control group (6.6±0.2.9 Pmol) (P=0.000). AAC was observed in 16 (40%) patients in CKD predialysis group, whereas in CKD on HD group, 26 (65%) patients had AAC. AVC was observed in 14 (35%) patients in CKD predialysis group, whereas in CKD on HD group, 21 (52.5%) patients had AVC. Using binary regression analysis, sclerostin was identified as an independent predictor for the presence of AAC (OR: 1.017; P=0.000) and AVC (OR: 1.013; P=0.001) in patients with CKD.

Conclusion
Patients with CKD (predialysis and on HD) exhibit an increase in sclerostin levels. Sclerostin expansion correlated positively with vascular and valvular calcification. Sclerostin is an independent risk factor for heart valve calcification and AAC in patients with CKD.

Keywords:
abdominal aortic calcification, aortic valve calcification, chronic kidney disease, sclerostin, vascular calcification

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Introduction

Vascular calcification and bone fragility are common and interrelated health problems that affect patients with chronic kidney disease (CKD). Recently, sclerostin was suggested to play a significant role in CKD-related bone disease as they are known inhibitors of the Wnt pathway, thus preventing bone formation [1]. Sclerostin has been implicated in the pathogenesis of vascular calcification, which may promote the cardiovascular events of morbidity and mortality in patients with CKD. However, the role of sclerostin in vascular calcification and clinical prognosis in CKD remains elusive [2,3]. Guidelines on CKD-mineral and bone disorder recommend the utilization of lateral lumbar abdominal radiograph to detect the presence or absence of vascular calcification and suggested that echocardiogram can be used to detect the vascular calcification (VC) in hemodialysis (HD) patients as acceptable alternative to computed tomography-based imaging. Many studies have been done to assess the relation between sclerostin and VC in patients with CKD, but the results were inconsistent. Some studies have found positive associations [4,5], whereas others

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have found no association [6] or negative associations [7,8]. Our study aimed to assess circulating levels of sclerostin in CKD predialysis group and on HD group and their relation to vascular calcification detected by lateral radiography on abdominal aorta and aortic valve calcification (AVC) echocardiography for detecting aortic valve calcification.

Patients and methods

This cross-sectional study was approved from the Ethical Committee of Faculty of Medicine, Menoufia University, and the patients gave an informed consent for participating in the study during the period from July 2018 till January 2019.

Those with a history of autoimmune disease, anticipated living kidney donation, permanent or current atrial fibrillation, immobility, or less than three hemodialysis sessions per week were excluded.

Participants were classified into three groups: group ? (control group) (*N*=15) included apparently normal individuals, group III (*N*=40) included patients with CKD not on HD (predialysis group I), and group II (*N*=40) included patients with CKD on regular HD for more than 6 months.

All patients underwent full history taking and clinical examination, and BMI was calculated as body weight (in kg) divided by height (in kg/m^2). Laboratory data included complete blood picture analyzed in an automated ADVIA-2120 hematological analyzer. Data on mineral bone disease (corrected serum calcium, phosphorus, intact PTH, and bone-specific alkaline phosphatase) were analyzed in AU480 (BECK Man, USA) analyser. Calcium–phosphorus product (Ca×P) was calculated, and renal function tests (blood urea and serum creatinine) were analyzed in Integra 400 autoanalyzer (Integra, Germany). C-reactive protein (CRP) was assessed by Turbidimetry, and EDTA tube was used for enzyme-linked immunosorbent assay analysis of sclerostin. Glomerular filtration rate (GFR) was calculated using CKD-EPI equation. Radiological investigations included vascular calcifications assessed by lateral lumbar radiograph of abdominal aorta. The radiograph was taken, and scores were graded as per the description of techniques and grading defined by Kauppila *et al*. [9], in which the severity of abdominal aortic calcification (AAC) was calculated from the level of L1–L4 lumbar vertebral segment graded on a 0–3 scale (range: 0–24). Echocardiography was used to detect the presence or absence of AVC.

Statistical analysis

Data entry, coding, and analysis were conducted using SPSS (20), released 2011, IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, New York, USA). Description of quantitative variables was in the form of mean and SD, and description of qualitative variables was by frequency and percentage. χ^2-test was used to assess the relationship between two qualitative groups. Analysis of variance test was used to measure the differences among three or more quantitative variables. Post Hoc test was used to measure the differences between each individual two means in cases of significant analysis of variance result. Pearson correlation (*r*) was used to assess the relations between quantitative variables, and binary regression analysis was performed to determine the possible predictor for vascular and valvular calcification among potential risk factors. *P* value less than 0.05 was considered significant. Receiver operating characteristic curve was used to estimate the cutoff level of sclerostin, with sensitivity and specificity, with respect to radiography and ECHO.

Results

In the current study, the mean age of control group was 51.8±10.7 years, for CKD predialysis group was 58.2 ±15.6 years, and for CKD on hemodialysis group was 46.02±17.8 years. There was no statistically significant difference among the three studied groups regarding age. There were seven males and eight females in the control group, predialysis group had 24 males and 16 females, and CKD on hemodialysis group had 18 males and 22 females. There was no statistically significant difference among the three studied groups regarding sex. There was a significant difference among the studied groups regarding BMI (*P*=0.01) (Table 1).

There were significant differences among the three studied groups regarding hemoglobin, low-density lipoprotein (LDL), calcium, phosphorus, calcium phosphorus score, intact PTH, bone-specific alkaline phosphatase, and CRP, but there were no significance differences between different studied groups regarding cholesterol, high-density lipoprotein (HDL), and triglycerides serum levels of participants. The mean value of sclerostin levels among the CKD on HD patients was significantly higher than that of CKD predialysis group which in turn was statistically higher than that of control group (*P*=0.000). AAC score by lateral abdominal radiograph was significantly higher in CKD pre-dialysis group compared with CKD on HD group (*P*=0.034) (Table 2).

Table 1 Sociodemographic characteristics of studied groups

	Control group (n=15)	CKD predialysis group (n=40) (mean±SD)	CKD on HD group (n=40) (mean±SD)		P value	Post-hoc test
Age (years) (mean±SD)	51.8±10.7	58.2±15.6	46.02±17.8	ANOVA test=2.1	0.1	P_1=0.6 P_2=0.8 P_3=0.09
Sex [n (%)]						
Male	7 (46.7)	24 (60.0)	18 (45.0)			
Female	8 (53.3)	16 (40.0)	22 (55.0)	χ^2=1.9	0.3	
BMI (kg/m^2) (mean±SD)	23.01±2.6	23.9±4.08	26.3±4.7	χ^2=4.7	0.01*	P_1=0.7 P_2=0.02* P_3=0.03*

ANOVA, analysis of variance; CKD, chronic kidney disease; HD, hemodialysis; P_1, comparison between control and CKD predialysis groups; P_2, comparison between control and CKD on HD groups; P_3, comparison between CKD predialysis and CKD on HD group. *Significant difference (P<0.05). **Highly significant difference (P<0.01).

Table 2 Comparison between studied groups regarding laboratory investigations and calcification score

	Control group (n=15)	CKD predialysis group (n=30)	CKD on HD group (n=30)	ANOVA test	P value	Post-hoc test
Hemoglobin (g/dl)	13.1±0.5	10.1±1.4	10.1±1.4	34.2	0.000**	P_1=0.000** P_2=0.000** P_3=0.9
Cholesterol(mg/dl)	176.2±21.4	160.6±47.1	187.7±38.7	0.5	0.6	P_1=0.8 P_2=0.9 P_3=0.5
Triglycerides (mg/dl)	112.6±36.7	141.5±34.6	127.4±47.3	3.1	0.05	P_1=0.05 P_2=0.4 P_3=0.2
LDL (mg/dl)	79.3±15.3	98.8±28.3	123.2±35.1	13.7	0.000**	P_1=0.08 P_2=0.000** P_3=0.001**
HDL (mg/dl)	38.1±10.7	34.7±7.5	42.01±19.6	2.5	0.08	P_1=0.7 P_2=0.6 P_3=0.06
Calcium (mg/dl)	9.9±0.6	8.07±0.6	8.6±0.7	35.5	0.000**	P_1=0.000** P_2=0.000** P_3=0.001**
PO_4 (mg/dl)	3.1±0.4	4.7±1.1	4.3±1.6	1.08	0.000**	P_1=0.000** P_2=0.000** P_3=0.7
Ca×PO_4	31.4±5.5	38.3±7.7	42.5±14.3	5.8	0.004**	P_1=0.09 P_2=0.000** P_3=0.2
iPTH (pg/dl)	32.1±15.01	313.3±546.6	507.2±532.7	5.1	0.000**	P_1=0.03** P_2=0.000** P_3=0.1
Bone-specific alkaline phosphatase (ng/ml)	13±5.5	38.7±17.8	100.1±115.1	10.1	0.000**	P_1=0.03* P_2=0.000** P_3=0.000**
CRP (mg/l)	5±0.8	16.7±2.6	28.3±31.7	6.01	0.003**	P_1=0.2 P_2=0.004** P_3=0.06
Sclerostin (pmol/l)	7.1±3.1	28.6±36.2	116.8±103.6	20.5	0.000**	P_1=0.03** P_2=0.000** P_3=0.000**
Score No of AAC by radiography		4.12±0.88	3.53±0.81	2.198	0.034*	

ANOVA, analysis of variance; CKD, chronic kidney disease; HD, hemodialysis. *Significant difference (P value < 0.05). **Highly significant difference (P value < 0.01).

Prevalence of calcification

AVC was detected in 14 (35%) patients of CKD predialysis group, whereas 21 (52.5%) patients in CKD on HD group had AVC. AAC was detected in 16 (40%) patients of CKD predialysis group, whereas in 26 (65%) patients of CKD on HD group (Table 3).

Correlation between sclerostin and other parameters

There was a highly significant positive correlation (r=0.4) between serum sclerostin level and age (P=0.000), highly significant positive correlation (r=0.402) between serum sclerostin level and bone-specific alkaline phosphatase (P=0.000), highly significant positive correlation (r=0.279) between serum sclerostin level and HDL (P=0.003), and highly significant positive correlation (r=0.353) between serum sclerostin level and LDL (P=0.000). There was a significant negative correlation (r=−0.189) between serum sclerostin level and calcium (P=0.047) (Table 4).

Comparison between demographic details and laboratory variables of all studied patients with chronic kidney disease (predialysis and on HD) with and without aortic valve calcification

There was a highly significant positive association between calcium, bone alkaline phosphatase, and sclerostin and the presence of AVC in all studied patients with CKD (Table 5).

Binary logistic regression analysis regarding aortic valve calcification

The significant independent risk factors for AVC were calcium and sclerostin. There was a highly significant

Table 3 Comparison among the three studied groups regarding prevalence of aortic valve calcification by ECHO and abdominal aortic calcification prevalence by lateral radiography on abdominal aorta

	Groups			χ^2-test	*P* value
	CKD on HD group (*n*=40)	CKD predialysis group (*n*=40)	Control group (*n*=15)		
Aortic valve calcification by ECHO					
No					
Frequency	19	26	15	13.01	0.000**
%	47.5	65.0	100.0		
Yes					
Frequency	21	14	0		
%	52.5	35.0	0.0		
Calcification prevalence of abdominal aorta by radiography					
No					
Frequency	14	24	15	19.1	0.000**
%	35.0	60.0	100.0		
Yes					
Frequency	26	16	0		
%	65.0	40.0	0.0		

CKD, chronic kidney disease; HD, hemodialysis. **Highly significant difference (*P* value < 0.01).

Table 4 Correlation between serum sclerostin and different parameters in all studied patients with chronic kidney disease (predialysis, and HD) (*n*=80)

	Sclerostin	
Variables	*r*	*P*
Age (years)	0.4	0.000**
BMI (kg/m^2)	0.02	0.8
Hemoglobin (g/dl)	–0.1	0.2
Calcium (mg/dl)	–0.189-	0.047*
PO_4 (mg/dl)	0.163	0.089
iPTH (pg/dl)	0.138	0.150
Bone-specific alkaline phosphatase (ng/ml)	0.402	0.000**
Cholesterol (mg/dl)	0.070	0.470
HDL (mg/dl)	0.279	0.003**
TG (mg/dl)	0.000	0.998
LDL (mg/dl)	0.353	0.000**
Ca×P	0.110	0.254
CRP (mg/l)	0.09	0.3

CRP, C-reactive protein; HD, hemodialysis; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerides. *Significant difference (*P* value < 0.05). **Highly significant difference (*P* value < 0.01).

positive association between AVC and calcium (OR: 0.276; *P*=0.004), and a highly significant positive association between AVC and sclerostin (OR: 1.013; *P*=0.001) (Table 6).

Comparison between demographic details and laboratory variables of all studied patients with chronic kidney disease (predialysis and on HD) with and without abdominal aortic calcification

There was a highly significant positive association between phosphorus and sclerostin and the presence of AAC in all studied patients with CKD (Table 7).

Table 5 Comparison between demographic details and laboratory variables of all studied patients with chronic kidney disease (predialysis and HD) with and without aortic valve calcification (*n*=80)

Variables	Patients without AVC (*n*=45) (mean ±SD)	Patients with AVC (*n*=35) (mean±SD)	*t*-Test	*P* value
Age (years)	54.24±15.31	50.37±16.06	1.098	0.275
BMI (kg/m^2)	24.84±4.26	25.56±4.96	–0.688	0.493
Hb (g/dl)	10.17±1.42	9.91±1.4	0.792	0.431
CRP (mg/dl)	23.31±24.7	21.02±27.7	0.388	0.699
Ca (mg/dl)	8.54±0.68	8.12±0.83	2.503	0.014**
PO_4 (mg/dl)	4.62±1.34	5.22±1.46	–1.889	0.063
iPTH (pg/dl)	403.06 ±445.22	410.68 ±544.22	–0.069	0.945
Bone spesific alkaline. phosphatase (ng/ml)	51.62±32.43	92.29 ±124.26	2.109	0.038*
Sclerostin (pmol/l)	36.36±59.83	119.47 ±98.90	4.652	0.000**
Cholesterol (mg/dl)	168.86±49.32	181.01 ±38.17	–1.203	0.233
HDL (mg/dl)	37.53±12.45	39.48±18.34	–0.565	0.574
TG (mg/dl)	135.57±39.88	133.143 ±44.73	0.257	0.798
LDL(mg/dl)	107.77±35.61	115.26 ±31.84	–0.976	0.332
Ca×P	40.027±12.55	40.92±10.54	0.341	0.734

CRP, C-reactive protein; Hb, HD, hemodialysis; hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerides. *Significant difference (*P* value < 0.05). **Highly significant difference (*P* value < 0.01).

Binary logistic regression analysis regarding abdominal aortic calcification

The significant independent risk factor for AAC was sclerostin. There was a highly significant positive

Table 6 Binary logistic regression analysis regarding aortic valve calcification calcification

	B	Signficance	Odds ratio	95% CI for odds ratio	
				Lower	Upper
Calcium (mg/dl)	−1.287	0.004**	0.276	0.114	0.669
Bone spesific alkaline phosphatase (ng/ml)	0.009	0.208	1.009	0.995	1.024
Sclerostin (pmol/l)	0.013	0.001**	1.013	1.005	1.021
Constant	8.982	0.013	7.962		

CI, confidence interval. **Highly significant difference (*P* value < 0.01).

Table 7 Comparison between demographic details and laboratory variables of all studied patients with chronic kidney disease (predialysis, and HD) with and without abdominal aortic calcification (*n*=80)

Variables	Patients without AAC (*n*=38) (mean ±SD)	Patients with AAC (*n*=42) (mean ±SD)	*t*-Test	*P* value
Age (years)	51.97±15.96	53.07±15.56	−0.311	0.756
BMI (kg/m^2)	24.3±4.32	25.9±4.69	−1.618	0.110
Hb (g/dl)	10.2±1.48	9.9±1.36	0.965	0.338
CRP (mg/dl)	18.1±20.1	26.1±30.03	−1.386	0.170
Ca (mg/dl)	8.5±0.78	8.2±0.75	1.535	0.129
PO_4 (mg/dl)	4.4±1.36	5.2±1.47	4.5	0.003**
iPTH (pg/dl)	412.2±443.69	401.14±529.77	0.101	0.920
Bone-spesific alkaline phosphatase (ng/ml)	50.28±31.99	86.72±114.7	−1.892	0.062
Sclerostin (pmol/l)	35.7±58.77	106.16±98.7	−3.825	0.000**
Cholesterol (mg/dl)	169.27±48.9	178.6±41.06	−0.928	0.356
HDL (mg/dl)	37.28±10.05	39.39±18.81	−0.616	0.539
TG (mg/dl)	132.44±40.9	136.38±43.02	−0.418	0.677
LDL (mg/dl)	109.36±31.97	112.58±36.07	−0.421	0.675
Ca×p	40.51±13.0	40.33±10.4	0.071	0.944

CRP, C-reactive protein; Hb, hemoglobin; HD, hemodialysis; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerides. **Highly significant difference (*P* value < 0.01).

Table 8 Binary logistic regression analysis regarding abdominal aortic calcification calcification

	B	Significance	Odds ratio	95% CI for odds ratio	
				Lower	Upper
PO_4 (mg/dl)	0.762	0.305	2.143	0.499	9.202
Sclerostin (pmol/l)	0.017	0.000**	1.017	1.008	1.025
Constant	−6.750-	0.632	0.003		

CI, confidence interval. **Highly significant difference (*P* value < 0.01).

association between AAC and sclerostin (OR: 1.017; *P*=0.000) (Table 8).

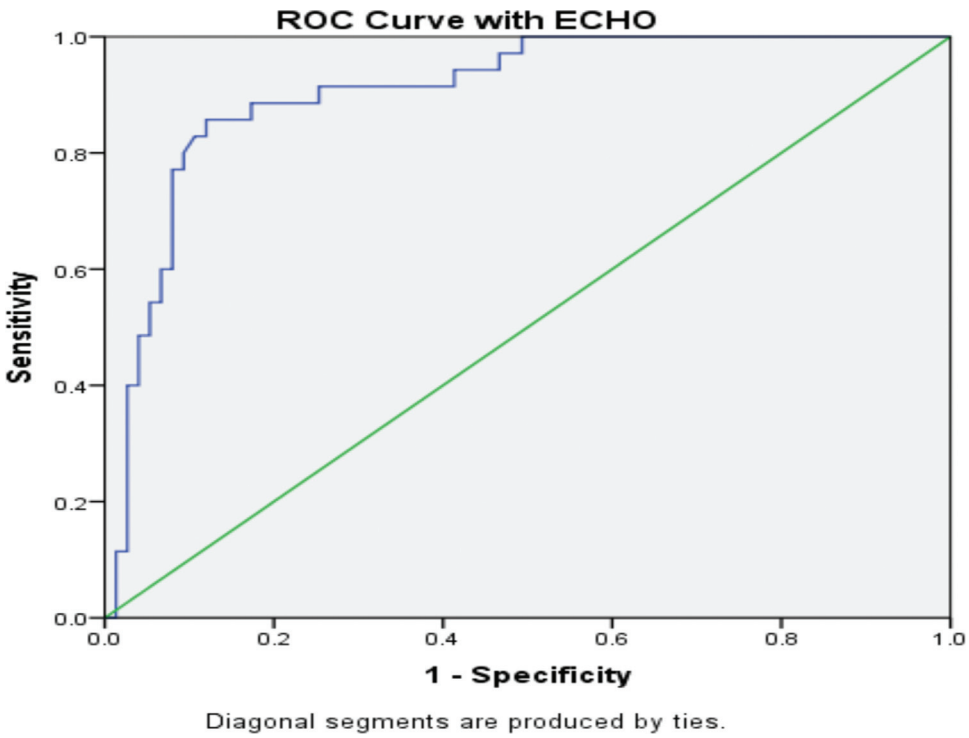
Receiver operating characteristic curve assessment of sclerostin in relation to abdominal aortic calcification by radiography and aortic valve calcification by ECHO

Serum sclerostin at a cutoff level of less than or equal to 19.60 can detect the presence of AVC by ECHO with 91% sensitivity and 69% specificity, with area under the curve of 0.906 (*P*=0.00). Sclerostin at a cutoff level less than or equal to 16.95 can detect the presence of AAC by radiography with 95% sensitivity and 67% specificity, with area under the curve of 0.911 (*P*=0.000) (Figs 1 and 2).

Discussion

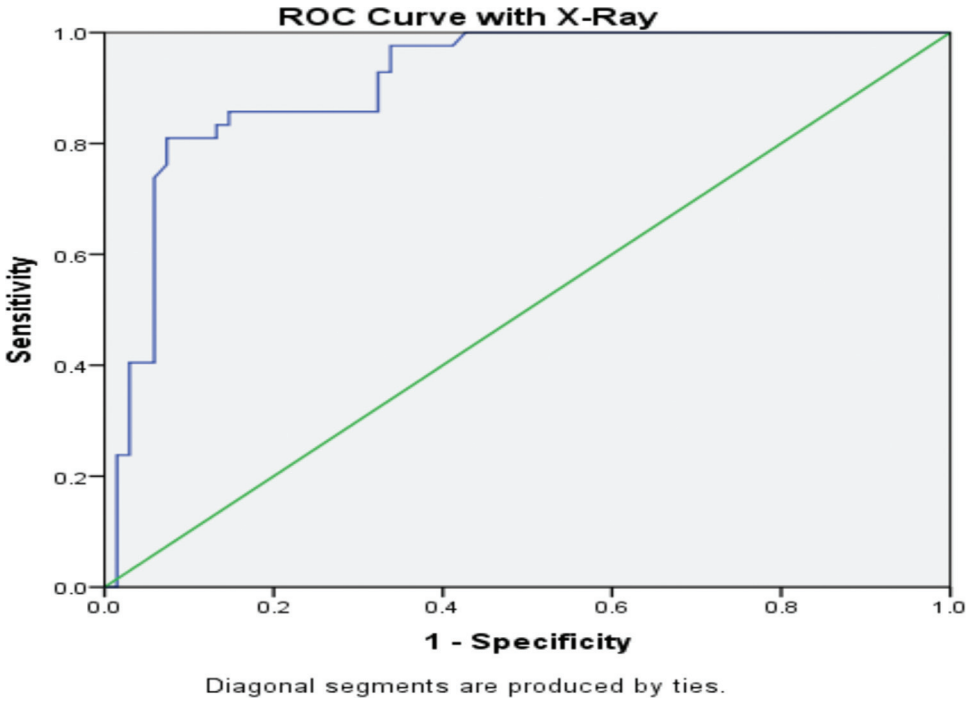
Patients with CKD are at tenfold higher risk of developing cardiovascular disease than age-matched controls. Being responsible for 54% of the deaths of patients with ESRD, cardiovascular mortality is the main cause of mortality among patients receiving HD [10]. Patients with CKD exhibit accelerated calcification of the intima, media, heart valves, and likely the myocardium as well as the rare condition of calcific uremic arteriolopathy (calciphylaxis) [11]. Recently, mechanisms of VC have been further elucidated, and many of the pathways involved could be amplified in patients with CKD such as FGF-23/Klotho axis, Wnt pathways, PI3K/Akt signaling, P38MAPK signaling pathway, and microRNAs [12]. The main action of sclerostin is to prevent frizzled proteins from colonizing the bone and to block Wnt signaling to reduce osteoblast genesis and bone formation. Thus, sclerostin may have a negative feedback role in osteoblast signaling at the onset of osteoid mineralization [13]. The

Figure 1



Receiver operating characteristic curve assessment of sclerostin in relation to aortic valve calcification by ECHO.

Figure 2



Receiver operating characteristic curve assessment of sclerostin in relation to abdominal aortic calcification by radiography.

precise mechanism by which elevated sclerostin levels affect VC remains unknown. It is also unclear whether the increase in serum sclerostin level may be owing to increased skeletal production or extraosseous production due to diminished renal clearance, or both [14]. It is now evident that VC follows a pathological pathway that is similar to physiologic bone process [15]. It was assessed that sclerostin production derives not exclusively from osteocyte cells from skeleton but also through

upregulation in vascular cells previously transformed to osteocytic phenotype after osteogenic regulation, such as has been shown in vascular smooth muscle cells under calcifying conditions [16]. Interestingly, the VC process will secrete sclerostin, a hormone that may act not only locally in the artery wall to reduce mineralization but will also destroy bone mineralization. These problems will lead to reduced bone mass, with a cycle between bone turnover and VC [17].

Diagnosis of vascular and valvular calcifications can be provided by ultrasound or plain radiograms. Echocardiography is crucial in detecting and staging both mitral and aortic calcifications, and it is fundamental to the evaluation of younger patients with CKD and those awaiting a kidney transplant [18]. So the aim of the present is to determine serum sclerostin levels in patients with CKD not on dialysis and those on regular hemodialysis and its role in vascular calcification.

The present study showed that patients with CKD (predialysis and on HD) exhibited an increase in sclerostin levels. Sclerostin expansion correlated positively with vascular calcification, and was an independent risk factor for heart valve calcification and AAC in patients with CKD. We found that the mean value sclerostin levels among the CKD on HD group was significantly higher that CKD predialysis group, which in turn was statistically higher than the control group (P=0.000). There was a significant increase in sclerostin level with decrease in GFR. This agrees with Mohamed *et al.* [19], who reported that sclerostin level is 1.5 folds higher in HD compared with control group, and El-Said *et al.* [20], who reported that sclerostin level in HD patients was higher than normal comparative group of matched age and sex, and also, other studies [21–23] agree with our results. There was a highly significant positive correlation (r=0.4) between serum sclerostin level and age (P=0.000). Pelletier *et al.* [24] reported that age was significantly and positively correlated with serum sclerostin (r=0.34; P=0.01). Mödder *et al.* [25] have reported that serum sclerostin increases with aging. Higher serum sclerostin levels might be associated with older age owing to diminished physical activity and clearance. There was a highly significant positive correlation (r=0.402) between serum sclerostin level and bone-specific alkaline phosphatase (P=0.000). Yang *et al.* [7] reported that the circulating sclerostin level was inversely associated with serum ALP (r=–0.235, P=0.008). There was a significant negative correlation (r=–0.189) between serum sclerostin level and calcium (P=0.047). Ji *et al.* [22] reported that serum sclerostin showed negative correlations with blood calcium. There was a highly significant positive correlation between serum sclerostin level and HDL (P=0.003) and a positive correlation between serum sclerostin level and LDL (P=0.000). Urano *et al.* [26] have demonstrated that the circulating sclerostin levels were associated with fat mass, HDL and LDL, cholesterol, uric acid, and homocysteine levels. These findings suggest some roles for sclerostin and Wnt/catenin signaling in the pathogenesis of metabolic diseases. There was no further significant relation between sclerostin and hemoglobin, BMI, parathyroid hormone, serum phosphorus, CRP, TG, and calcium×phosphorus. In comparison between demographic details and laboratory variables of all studied patients with CKD (predialysis and HD) with and without AVC. The mean calcium level among patients with CKD with AVC was 8.12±0.83, which was significantly lower than those without AVC (8.54±0.68) (P=0.014). The mean level of bone-specific alkaline phosphatase level among patients with CKD with AVC was 92.29 ±124.26 which was significantly higher than those without AVC (51.62±32.43) (P=0.038). Ishimura *et al.* [27] also found that BAP was significantly associated with vascular calcification. The mean sclerostin level among patients with CKD with AVC was 119.47±98.90, which was significantly higher than those without AVC (36.36±59.83) (P=0.000). Wang *et al.* [4] found that patients with valve calcification had higher sclerostin levels compared with those without valve calcification (P=0.011). In binary regression analysis, only calcium and sclerostin levels were independently associated with AVC. There was a highly significant positive association between AVC and calcium (OR: 0.276; P=0.004) and a highly significant positive association between AVC and sclerostin (OR: 1.013; P=0.001). El-Said *et al.* [20] reported that there was a significant negative correlation between serum sclerostin level and degree of cardiac valve calcification in hemodialysis patients. Ji *et al.* [22] found that eGFR, phosphorus, sclerostin, and urea were independent risk factors influencing valve calcification by logistic regression analysis of valve calcification in CKD stages 3–5. In comparison between demographic details and laboratory variables of all studied patients with CKD (predialysis and on HD) with and without AAC. The mean phosphorus level among patients with CKD with AAC was 5.2±1.47, which was significantly higher than those without AAC (4.4 ±1.36) (P=0.003). Dhakshinamoorthy *et al.* [28]

reported that the mean phosphorus level among patients with CKD with AAC was 5.2±1.5 which was higher than those without AAC (4.9±1.6), but with no statistical difference (*P*=0.397). The mean sclerostin level (pmol/l) among patients with CKD with AAC was 106.16±98.7, which was significantly higher than those without AAC (35.7±58.77) (*P*=0.000). In binary regression analysis, only sclerostin level was independently associated with AAC. There was a highly significant positive association between AAC and sclerostin (OR: 1.017; *P*=0.000). Evenepoel and colleagues [29–31] reported that sclerostin levels were positively associated with VC. Wang *et al*. [4] in univariate analysis for AAC also reported that the presence of AAC was associated with sclerostin level (β=0.009; *P*=0.001), and high sclerostin levels were a determinant of AAC. Lv *et al*. [21] reported that, on multivariate analysis, only age and sclerostin level were independently associated with VC and were significant predictors of VC in patients with CKD. Regarding receiver operating characteristic curve assessment of sclerostin in relation to AAC by radiography and AVC by ECHO, we found radiograph to be more sensitive than ECHO. On the contrary, ECHO was found to be more specific than radiography. The measurement of serum sclerostin levels in clinical practice could be a novel strategy to establish early clinical interventions in high-risk individuals of cardiovascular disease. However, further studies are needed to confirm these results and to corroborate the role of sclerostin as a potential biomarker [32].

Our study had limitations: first, the cross-sectional design of the study made it difficult to drive a solid cause and effect relationship between sclerostin level and VC. Second, there was a smaller sample size across each group of CKD. A prospectively designed study would help to elucidate whether clinical interventions to modulate serum sclerostin would improve patient survival.

Conclusion

From our work, we showed that serum sclerostin levels was significantly increased with the decline in GFR. It were significantly higher in patients with CKD on HD than in CKD predialysis and healthy controls. Sclerostin level was associated with VC and valvular calcification in patients with CKD predialysis and on HD. However, VC is an extremely multifactorial process and a continuous process, and so far. there has been no identified single cause for the explanation of its pathophysiology. Therefore, we expect that sclerostin may be used as a potential contributor or biomarker of vascular calcification in CKD.

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Conflicts of interest

There are no conflicts of interest.

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