Sclerostin: Another Vascular Calcification Inhibitor?

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Context: Sclerostin, a Wnt antagonist produced by osteocytes, regulates osteoblast activity and is a well-established key player in bone turnover. Recent data indicate that the Wnt pathway may also be involved in vascular calcification.

Objective: The present study tests the hypothesis that serum sclerostin levels are associated with vascular calcification in patients with chronic kidney disease (CKD) not yet receiving dialysis.

Design, Setting, Participants, and Measurements: We performed a cross-sectional analysis in 154 patients with CKD. Aortic calcification (AC) was assessed by lumbar X-ray and scored with a maximum score of 24. In addition to traditional and nontraditional cardiovascular (CV) risk factors, serum sclerostin levels were assessed (ELISA). Regression analysis was performed to identify determinants of serum sclerostin and AC.

Results: AC was present in 59% of patients. Older age ($P < .0001$), male sex ($P = .006$), lower estimated glomerular rate (eGFR) ($P = .0008$), lower bone-specific alkaline phosphatase ($P = .03$), and the absence of AC ($P = .006$) were identified as independent determinants of higher serum sclerostin levels. In univariate logistic regression, higher age, diabetes, CV history, higher body mass index, higher serum C-reactive protein and sclerostin levels and lower estimated glomerular rate were all associated with the presence of AC. In multivariate analysis, lower, not higher, sclerostin levels ($P = .04$, odds ratio [OR] per ng/mL of 0.24), higher age ($P < .0001$, OR per year of 1.17) and CV history ($P = .02$, OR for a positive CV history of 3.83) were identified as independent determinants of AC.

Conclusions: In this cohort of patients with CKD, we found that patients with aortic calcifications (ACs) had higher sclerostin levels. However, in multivariate analysis, the association became inverse. Additional clinical and experimental studies are urgently required to clarify whether or not sclerostin protects against progression of vascular calcification. **(*J Clin Endocrinol Metab* 98: 3221–3228, 2013)**

Patients with chronic kidney disease (CKD) have a substantially increased risk of premature cardiovascular (CV) disease. Vascular calcification (VC) is highly prevalent in patients with CKD, even in patients with early disease (1–3). Both traditional (older age, diabetes, arterial hypertension, and CV disease) and nontraditional CV risk factors (inflammation, oxidative stress, and disordered mineral metabolism) contribute to a high calcification burden in CKD (1, 2, 4, 5). Vascular calcification is associated with adverse clinical outcomes, including ischemic cardiac events and subsequent CV mortality (6, 7). Once thought to be a passive degenerative process, considerable evidence now suggests that vascular calcification is regulated in a manner very similar to that of developing bone. Central in this process is the osteoblastic transition of vascular smooth muscle cells (8). The factors involved in this

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Abbreviations: AC, aortic calcification; BMI, body mass index; bsAP, bone-specific alkaline phosphatase; CKD, chronic kidney disease; CRP, C-reactive protein; CV, cardiovascular; eGFR, estimated glomerular rate; OR, odds ratio; VC, vascular calcification.

change in vascular smooth muscle cell phenotype have been the focus of much research in recent years, with evidence suggesting that it is driven by both an increase in factors that promote this change and a decrease in inhibiting factors (9–12). In recent times, a host of these calcification promoters and inhibitors have been identified with systemic or localized action. The relative importance of these factors remains unclear, and it is likely that some are more involved in the progression of soft tissue calcification than in its initiation (12).

The identification of a link between bone mass in humans and gain- or loss-of-function mutations in the Wnt coreceptor low-density lipoprotein receptor–related protein 5 or in the Wnt antagonist sclerostin has called the attention of scientists and clinicians to the importance of the Wnt signaling pathway in skeletal biology and disease (13). Recent clinical and experimental evidence indicates that the Wnt pathway may also play a prominent role in the process of vascular calcification (14–16).

Acknowledging that the main action of sclerostin is a decrease in bone formation and that sclerostin is up-regulated in the vascular wall during the vascular calcification process, it may be hypothesized that sclerostin is part of a local counterregulatory mechanism directed to suppress VC (17). Sclerostin produced in the vascular wall may spill over to the circulation and thereby contribute to circulating levels of the protein.

The aim of the present cross-sectional study of patients from across the entire spectrum of predialysis CKD was to investigate the association between circulating sclerostin levels and vascular calcification.

Patients and Methods

Patient population

A total of 154 patients with CKD were recruited from an ongoing longitudinal observational study evaluating the natural history of mineral metabolism (clinical trial registration no. NCT00441623). Patients were followed at the outpatient clinic of the University Hospitals Leuven, were 18 years of age or older, and were able to provide consent. The study was performed according to the Declaration of Helsinki and approved by the ethics committee of the University Hospital Leuven. Informed consent was obtained from all patients. Demographic and clinical data were extracted from electronic patient files. Hyperlipidemia was defined as total cholesterol >200 mg/dL and/or low-density lipoprotein cholesterol >100 mg/dL or statin intake. Hypertension was defined as blood pressure greater than 140/90 mm Hg and/or treatment of hypertension. CV history was defined as history of myocardial infarction, percutaneous coronary artery intervention, cardiac surgery, peripheral artery disease, or cerebrovascular disease.

Biochemical measurements

Blood samples were collected in the outpatient clinic at time of enrollment and immediately analyzed for creatinine, hemoglobin, calcium, phosphate, C-reactive protein (CRP), cholesterol, PTH, calcitriol, and calcidiol. In addition, serum and plasma were aliquoted and stored at −80°C until further analysis. Creatinine, hemoglobin, calcium, phosphate, CRP, and cholesterol were all measured using standard laboratory techniques. Serum 1,25-dihydroxyvitamin D (calcitriol) and 25-hydroxyvitamin D (calcidiol) levels were measured using a RIA. Serum full-length PTH levels were determined by an immunoradiometric assay, as described elsewhere (18). Bone-specific alkaline phosphatase (bsAP) was measured using an electrophoretic method (ISOPAL; Analis, Sint-Denijs-Westrem, Belgium). To assess bone resorption, serum C-terminal cross-linked telopeptide was measured using an electrochemiluminescence immunoassay (b-CrossLaps/serum; Roche Diagnostics, Basel, Switzerland). Albumin was measured using the bromocresol green method. Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI equation. CKD stages were divided into mild (CKD stages 1 and 2); moderate (CKD stage 3), and severe CKD (CKD stages 4 and 5). Serum sclerostin was measured by ELISA (TECOmedical; Demeditec Diagnostics GmbH, Kiel-Wellsee, Germany) according to the manufacturer's instructions. The limit of detection of this assay is 0.015 ng/mL; the lower and upper limit of quantification are, respectively 0.17 and 4.88 ng/mL.

VC

Calcification of the aorta was graded using a previously validated system in which both the location and the severity of calcific deposits at each lumbar vertebral segment (L1–L4) were evaluated (19). The composite score (ie, the summation of scores of individual aortic segments both for the anterior and posterior wall) has a maximum of 24. This composite score is further referred to as sum AC. A single reader (S.H.), blinded to the clinical background of the patients, analyzed all lateral lumbar radiographs.

Statistical analysis

Continuous variables are expressed as means (SD) for normally distributed variables or median (minimum–maximum) otherwise. Differences between groups were analyzed using a parametric or nonparametric 1-way ANOVA, with post hoc correction for multiple comparisons, as appropriate. Associations between serum sclerostin and clinical and biochemical parameters were studied with Spearman rank correlation and univariate and multivariate linear regression. Parameters that were not normally distributed, including sclerostin, were log-transformed. Univariate and multiple regression with backward selection was used to model the risk factors for aortic calcification (AC) and sclerostin. Sclerostin and AC were assessed as both continuous and categorical variables (above and below the median). The SAS version 9.2 (SAS Institute, Cary, North Carolina) software program was used for the statistical analysis. Two-sided P values $<.05$ were considered statistically significant.

Results

Demographics

Patient demographics and relevant clinical and biochemical parameters are summarized in Table 1. Of the

Table 1. Demographics in the Whole Population and According to CKD Stage

	CKD Stage				
	All	**1–2**	**3**	**4–5**	***P* Value**
No.	154	40	46	68	
Age, y	59.7 ± 15	46 ± 11	64 ± 12	65 ± 14	<.0001
Male sex, %	58	70	63	49	.07
Diabetic, %	21	15	28	18	.2
Vascular history, %	29	7.5	28	42	.0005
BMI, kg/m^2	27 ± 5	26 ± 3.6	28.3 ± 5	26.6 ± 5	.02
Hyperlipidemia, %	81	68	80	88	.04
eGFR, mL/min/1.73 m^2	34 (5–119)	83 (61–119)	39 (30–58)	21 (5–30)	<.0001
Total cholesterol, mg/dL	174 ± 33	174 ± 26	180 ± 39	171 ± 32	.3
Calcium, mg/dL	9.3 ± 0.48	9.3 ± 0.5	9.3 ± 0.4	9.3 ± 0.5	.6
Phosphorus, mg/dL	3.3 ± 0.7	2.98 ± 0.62	3.2 ± 0.6	3.6 ± 0.7	<.0001
CRP, mg/L	1.4 (0.6–52.9)	0.9 (0.6–42.6)	2.4 (0.6–52.9)	1.9 (0.6–46.5)	.04
25-Hydroxyvitamin D, μg/L	27 (3.5–77.2)	21.6 (7.1–54.9)	26.6 (9.7–56.1)	30.3 (3.5–77.2)	.01
1,25-Dihydroxyvitamin D, ng/L	42 (14.2–110)	57.8 (26.0–110)	44.1 (22.7–75.3)	38.6 (14.2–93.9)	.0004
24-h proteinuria, g/24 h	0.32 (0.04–6)	0.15 (0.04–2.3)	0.29 (0.05–3.4)	0.59 (0.05–6)	.001
PTH, ng/L	48 (0.1–322)	16.7 (0.1–45.3)	33 (8–106)	61.8 (0.1–322)	<.0001
Sclerostin, ng/mL	0.67 (0.3–0.8)	0.48 (0.23–0.87)	0.68 (0.26–1.35)	0.83 (0.2–2.07)	<.0001
bsAP, U/L	21.5 (6–64)	20 (6–55)	21 (6–46)	24 (8–64)	.13
CTX, ng/L	444 (54–2298)	216 (54–676)	388 (120–936)	758 (180–2298)	<.0001
Systolic BP, mm Hg	140 (100–190)	134 (110–170)	145 (100–175)	142 (103–190)	.11
Diastolic BP, mm Hg	80 (50–115)	80 (70–90)	80 (65–98)	80 (58–90)	.04
Sum AC	2 (0–21)	0 (0–9)	3 (0–21)	4 (0–17)	<.0001
Presence of VC, %	58.97	27.5	70.2	69.6	.0002
Statin, %	60	40	61	71	.0004
No. of antihypertensive drugs	2 (0–6)	1 (0–3)	2 (0–6)	2 (0–5)	<.0001

Abbreviations: BP, blood pressure; CTX, C-terminal cross-linked telopeptide; Hct, hematocrit.

154 patients included, 58% were men, and 21% were diabetic. The mean age was 60 ± 15 years, and the mean eGFR was 34 ml/min/1.72 m^2. The primary renal disease was diabetes in 5.3%, glomerulonephritis/vasculitis in 36.3%, interstitial nephritis in 17.4%, cystic/hereditary/congenital in 7.9%, vascular disease in 21%, and unknown or missing in 12.1% of patients.

Determinants of serum sclerostin levels

Table 2 shows clinical and biochemical determinants in patients with sclerostin levels above and below the median. Patients with sclerostin levels above the median were characterized by older age, lower eGFR, lower total cholesterol level, higher serum phosphorus level, lower bsAP level, higher calcification score, and more CV burden. In multivariate logistic regression analysis, older age (odds ratio [OR], 1.085; 95% confidence interval, 1.051–1.121) was found to be independently associated with sclerostin levels above the median. Similar associations were observed when sclerostin was assessed as a continuous variable. In univariate linear regression analysis, the presence of calcification, older age, higher PTH and phosphate levels as well as lower eGFR and lower bsAP, total cholesterol, and calcitriol levels were associated with higher sclerostin levels. In multivariate regression analysis, older age ($P < .0001$), male sex ($P = .006$), lower eGFR ($P = .0008$), the absence of calcification ($P = .006$), lower bsAP levels ($P = .03$), and lower cholesterol levels ($P = .03$) were identified as independent determinants of higher levels of circulating sclerostin. Given the known sex effect in both the general population and patients with CKD, sex was forced into the multivariate linear regression model even though no significant association was found in univariate analysis (20, 21).

Determinants of AC in CKD

AC was observed in 59% of the patients. The prevalence of AC was highest in patients with advanced CKD stage: AC was present in 27.5% of patients with CKD stages 1 and 2 and in 70.0% patients with CKD in stages 3 and 4 (Table 1). Table 3 compares clinical and biochemical parameters between patients with and without AC. Patients with AC were older and had a higher body mass index (BMI) and lower eGFR. A higher percentage of patients with AC were diabetic and had a history of CV events. Interestingly, patients with AC had not only higher PTH and CRP levels but also higher sclerostin levels. Sclerostin levels were highly correlated with age ($r = 0.53$, $P < .0001$), in CKD patients both with ($r = 0.34$, $P = .001$) and without AC ($r = 0.68$, $P < .0001$).

In univariate logistic regression, older age, diabetes, CV history, higher BMI, and higher CRP and sclerostin levels

Table 2. Demographics and Biochemistry According to Values Below and Above Median Sclerostin

	Below Median	Above Median	*P* Value
Demographics			
Age, y	53 ± 15	77 ± 11	<.0001
Men, %	57	59	.7
Diabetes, %	16	25	.16
Vascular history, %	16	43	.0002
Hyperlipidemia, %	76	84	.2
BMI, kg/m^2	27 ± 5.4	27 ± 4.4	.9
Biochemical			
eGFR, mL/min/1.72 m^2	46.8 (10–119)	27.3 (5–97)	<.0001
Hct, %	40.5 ± 4.8	40.5 ± 4.5	.13
Total cholesterol, mg/dL	179 ± 32	169 ± 33	.0213
Calcium, mg/dL	9.3 ± 0.44	9.3 ± 0.5	.7
Phosphorus, mg/dL	3.2 ± 0.7	3.5 ± 0.7	.0053
CRP, mg/L	1.3 (0.6–52.9)	1.8 (0.6–23.2)	.7
25-Hydroxyvitamin D, μg/L	26.1 (3.5–77.2)	27.9 (7.1–71.8)	.1
1,25-Dihydroxyvitamin D, ng/L	45.8 (20–110)	40.6 (14.2–87)	.06
bsAP, U/L	24 (6–64)	19 (6–46)	.02
CTX, ng/L	442 (54–1616)	444.5 (90–747)	.9
Proteinuria, g/24 h	0.35 (0.05–5.7)	0.27 (0.04–5.9)	.26
PTH, ng/L	30.8 (3–322)	34.8 (0.1–203)	.35
Vascular parameters			
Systolic BP (mm Hg)	135.5 ± 23	141.1 ± 18.8	.19
Diastolic BP (mm Hg)	78.9 ± 6.9	77.34 ± 7.8	.23
Sum AC	0 (0–21)	3 (0–17)	.003

Abbreviations: BP, blood pressure; CTX, C-terminal cross-linked telopeptide; Hct, hematocrit.

and lower eGFR levels were all associated with the presence of AC (Table 4). In multivariate logistic regression analysis, older age ($P < .0001$, OR per year of 1.17), CV history ($P = .02$; OR for a positive vascular history of 3.83), and lower sclerostin levels ($P = .04$; OR per ng/mL of 0.24) were found to be independently associated with AC. No interaction between sclerostin and age was observed ($P = .8$). When we introduced sclerostin as a categorical variable into the model, the same inverse relationship of sclerostin ($P = .05$; OR for sclerostin below the median of 4.1) with AC was found, independent of age and CV history. Moreover, sclerostin levels were found to be significantly ($P = .05$) higher in 25 patients without calcifications compared with 25 patients with calcifications. These patients were matched (1:1) for age, sex, presence of diabetes, and eGFR.

Discussion

The main finding of the present study is that circulating sclerostin levels are significantly and independently associated with AC. The nature of this association, however, is complex.

Vascular calcification is highly prevalent in the elderly population and even more so in patients with CKD (1, 22). Given the important role of Wnt signaling in skeletal biology and disease and given the similarity between the process of bone formation and vascular calcification, we aimed to elucidate the interaction between the Wnt inhibitor sclerostin and vascular calcification. Sclerostin is a 22-kDa glycoprotein secreted almost exclusively by osteocytes and to a lesser extent by other cell types. It travels through osteocytic canaliculi to the bone surface and binds to low-density lipoprotein receptor–related protein-5 and -6 and inhibits the Wnt/β-catenin canonical signaling pathway, thereby decreasing osteoblastogenesis and bone formation (23, 24). In humans, the importance of sclerostin is highlighted by 2 genetic disorders associated with significant progressive increases in bone mass, namely, sclerosteosis (caused by a loss-of-function mutation in the gene encoding sclerostin, resulting in improperly spliced *SOST* mRNA) and Van Buchem disease (caused by a deletion of an enhancer element that is normally downstream of the *SOST* gene), respectively (25). Present understanding of the regulation of SOST/sclerostin expression and sclerostin metabolism is as yet incomplete.

In the present cross-sectional study of patients from across the entire spectrum of predialysis CKD, increased age, male sex, and absence of calcifications and lower eGFR were identified as independent determinants of increased serum sclerostin levels. The observation of a strong and independent association between age and sclerostin level confirms and extends data from previous studies in subjects without CKD (26–28). Serum scleros-

Table 3. Demographics and Biochemistry According to Presence or Absence of AC

	Calcification Present	Calcification Absent	*P* Value
Demographics			
Age, y	68.2 ± 10.2	49.5 ± 12.4	<.0001
Men, %	54.4	62.5	.3
Diabetes, %	27.1	7.8	.003
Vascular history, %	44.6	7.8	<.0001
Hyperlipidemia, %	83.7	75	.2
BMI, kg/m^2	27.7 ± 4.8	25.4 ± 4.9	.0008
Biochemical			
eGFR, ml/min/1.72 m^2	34.7 ± 21.9	55.9 ± 33.5	.0001
Hct, %	39 ± 5	41 ± 4	.09
Total cholesterol, mg/dL	173.4 ± 36.9	178.0 ± 30.6	.30
Calcium, mg/dL	9.3 ± 0.5	9.2 ± 0.5	.13
Phosphorus, mg/dL	3.4 ± 0.7	3.2 ± 0.6	.12
CRP, mg/L	2.3 (0.6–52.9)	1.10 (0.6–42.6)	.03
25-Hydroxyvitamin D, μg/L	26.7 (3.5–57.4)	26.5 (7.1–77.2)	.9
1,25-Dihydroxyvitamin D, ng/L	40.8 (16.4–86.7)	45.0 (14.2–110.3)	.3
Potassium, mmol/L	4.5 ± 0.5	4.3 ± 0.7	.04
24-h proteinuria, g/24 h	0.33 (0.04–5.04)	0.33 (0.05–5.9)	.7
PTH ng/L	40.9 (0.1–322.5)	26.0 (0.1–203.2)	.02
Sclerostin, ng/mL	0.73 (0.27–2.07)	0.56 (0.2–1.53)	.001
bsAP, U/L	20.5 (6–53)	22.5 (6–64)	.3
CTX, ng/L	454 (90–2298)	409 (54–616)	.5
Vascular parameters			
Systolic BP (mm Hg)	134.8 ± 18.8	129.3 ± 17.7	.05
Diastolic BP (mm Hg)	75.1 ± 10.2	79.5 ± 10.6	.02

Abbreviations: BP, blood pressure; CTX, C-terminal cross-linked telopeptide; Hct, hematocrit.

tin levels may increase by an average of 4-fold during a lifetime. The mechanisms underlying the positive association between age and sclerostin levels remain largely obscure. One possible explanation might be that low physical activity, specific to aging, induces a decrease in mechanical load thereby leading to an increase in serum sclerostin levels (26, 29). This is underscored by the increase in sclerostin levels in long-term immobilized patients (30). Clinical and subclinical vascular calcification is another hallmark of aging (31). It is important to acknowledge that the arterial vasculature is the second most extensively calcified structure in the human body after the skeleton. Recent experimental and clinical evidence demonstrates expression of sclerostin and Wnt in calcifying vascular tissues (vascular wall and heart valves) (15, 16). It is not known to what extent extraskeletal sclerostin, similar to sclerostin originating from the bone (32), might spill over to the circulation and contribute to systemic levels. In the present study, patients with vascular calcification exhibited significantly higher serum sclerostin lev-

Table 4. Factors Associated With AC in Univariate and Multivariate Logistic Regression Model.

	Unit Increase	Unadjusted OR (95% CI)	*P* Value	Final Model Adjusted OR (95% CI)[a]	*P* Values
Traditional risk factors					
Age	years	1.16 (1.11–1.21)	<.0001	1.17 (1.11–1.25)	<.0001
Diabetes	yes vs no	4.4 (1.7–13.7)	.005		
CV history	yes vs no	9.5 (3.8–29)	<.0001	3.83 (1.28–13)	.02
BMI	kg/m^2	1.11 (1.030–1.2)	.006		
Hypertension	yes vs no	4.24 (1.17–19.97)	.04		
Biochemical parameters					
eGFR	ml/min/1.72m^2	0.973 (0.96–0.99)	<.0001		
CRP (log)	mg/L	1.417 (1.04–1.94)	.03		
Sclerostin (log)	ng/mL	1.835 (1.19–2.84)	.0009	0.24 (0.06–0.87)	.04

Abbreviation: CI, confidence interval.

[a] ORs adjusted for the independent variables included in the final model, obtained after backward selection. Variables included in the final model were age, diabetes, CV history, hypertension, BMI, eGFR, CRP, and sclerostin.

els in univariate analyses. In line with our data, higher serum sclerostin levels have also been reported in patients with calcified aortic valves as compared with noncalcified counterparts (33).

Serum sclerostin levels also showed an inverse association with eGFR. It is not known whether this inverse association is due to retention, to decreased metabolism, or to increased production. Remarkably, sclerostin levels increased despite a concomitant increase of PTH, which previously has been shown to decrease sclerostin transcription both in vivo and in vitro (32, 34, 35). This discrepancy may be explained, at least partly, by the fact that CKD is a state of PTH resistance (36). Because vascular calcification is highly prevalent in CKD, it may be hypothesized, as indicated before, that increased extraskeletal (vascular) production also contributes to the increased circulating sclerostin levels in this patient population. In the present CKD cohort, vascular calcifications were observed in 59% of the patients. This value is in line with literature data (1–3). The reported prevalence rates, however, show a huge variation. This variation most probably reflects case-mix (comorbidity and age) and differences in sensitivity of the methods used to diagnose vascular calcification.

Importantly, in multivariate logistic regression analysis, higher circulating sclerostin levels were associated with a lower risk for vascular calcification, suggesting that circulating sclerostin may be a protective factor for (progression) of vascular calcification. Not unexpected, but at least reassuring, the absence of vascular calcification was also an independent determinant of higher sclerostin levels in multivariate analysis. These data support the notion that sclerostin may be part of a normal feedback mechanism, or, otherwise stated, may represent a counterregulatory mechanism to suppress the progression of vascular calcification. This line of reasoning is supported by experimental data showing overexpression of secreted frizzled related proteins, ie, another group of Wnt pathway inhibitors, in late but not early stages of vascular calcification in an experimental rat model (17). Our data furthermore corroborate with the results of a recent post hoc survival analysis in 100 prevalent hemodialysis patients showing that high circulating sclerostin levels are associated with improved survival (37). The question whether sclerostin may retard or halt the progression of vascular calcification is of critical importance as emerging therapies in the field of osteoporosis target Wnt inhibitors, including sclerostin.

Undoubtedly, our findings will actualize the intriguing question whether the presence of vascular calcification affects bone metabolism, ie, whether there is true crosstalk between the bone and the vasculature (12). A large number of studies have demonstrated a relationship between vascular disease and bone pathology. The coexistence of osteoporosis and features of atherosclerosis, particularly vascular calcification, has been consistently demonstrated and is most prevalent in postmenopausal women and elderly people (31). Recently, De Schutter et al (38) in an experimental study demonstrated cortical bone loss to occur concomitantly with the development of vascular calcifications. It may be hypothesized that sclerostin produced in the vascular wall may not only have beneficial paracrine effects (retard the progression of vascular calcification) but also, when spilled over to the circulation, may induce negative endocrine effects on the skeleton (decreased osteoblastogenesis and increased osteoclastogenesis) (24, 39). Thus, sclerostin might indeed be an important messenger in the bone-vascular axis. Interestingly, and counterintuitively, high sclerostin levels were found to be associated with higher bone mineral density (BMD) in both the general population and patients with CKD (21, 40, 41). A possible explanation for this positive association is that a higher bone mass implies more osteocytes and therefore higher sclerostin production.

The present study has several strengths and limitations. We are the first to investigate the relation between circulating sclerostin and aortic calcification in a rather large CKD cohort. The fact that we observed this association using a technique with a rather low sensitivity for detecting vascular calcification, ie, lateral lumbar, is remarkable and supports the robustness of our findings. The principal limitation of the present study was its cross-sectional design, and thus the causative nature of the associations between sclerostin and aortic calcification cannot be established. Furthermore, the lack of bone histomorphometry data and bone biomarkers can also be viewed as a limitation. However, our study will undoubtedly fuel further research regarding the influence of Wnt/β-catenin pathway, its inhibitor sclerostin, and the antisclerostin antibody in the pathogenesis of vascular calcification.

In conclusion, we observed higher sclerostin levels in patients with calcification in CKD not yet receiving dialysis presenting with aortic calcification. In the fully adjusted model, however, higher sclerostin levels were associated with less aortic calcification. In aggregate, our findings suggest that extraskeletal sclerostin might contribute substantially to circulating levels and might represent a counterregulatory mechanism to suppress the progression of vascular calcification. Additional clinical and experimental studies are urgently required to elucidate whether or not sclerostin protects against progression of vascular calcification.

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