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CASE SERIES

Assessment of Serum Sclerostin Level and its Relationship to Coronary Calcifications in Chronic Kidney Disease Patients

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Abstract

Background: **In individuals with chronic kidney disease (CKD) or end-stage renal disease, one of the leading causes of cardiovascular death is cardiovascular calcification. Serum sclerostin levels were shown to be elevated in individuals with CKD. Serum sclerostin levels in kidney illness patients are a reliable predictor of low-turnover bone disease, according to new research. Bone metabolism and osseous calcification are both regulated by several of these characteristics. The purpose of this study was to determine the relationship between CKD patients' serum sclerostin levels and coronary calcifications.**

Patients and methods: **CKD patients with GFR less than 60 ml/min who were on regular hemodialysis, as well as 20 CKD patients who were not on hemodialysis and a control group were compared in this case−control comparative research.**

Results: **Hemodialysis-dependent CKD patients have significantly higher coronary artery calcification (CAC) scores (Agatston scores) and calcific plaque than nonhemodialysis-dependent patients, as well as those who have been on hemodialysis for more than a year compared with those who have been on it for less than a year. They also have significantly higher serum sclerostin levels than healthy controls. A positive multi slice computed tomography (MSCT) scan for coronaries in individuals with CKD is associated with a higher risk of developing coronary artery disease. Patients with CAC score (Agatston units) that suggest vascular calcification had higher serum sclerostin levels. A high blood sclerostin level is linked to an increased risk of developing CAC.**

Keywords: Chronic kidney disease, Coronary artery calcification, End-stage renal disease

1. Introduction

Patients with chronic kidney disease (CKD), particularly those on hemodialysis, are at an increased risk of cardiovascular disorders such coronary artery disease, arrhythmias, and sudden cardiac death.

Patients with CKD who develop vascular calcification have a poor outlook for long-term survival as well as increased risk of cardiovascular disease and death.

Vascular calcification is well known to be controlled by a delicate balance between promoter and inhibitor regulatory proteins acting on the vessel wall directly and systemically in the circulation.

Sclerostin is one of the numerous biomarkers being researched as a possible biomarker for vascular calcification, which is associated with cardiovascular problems.

Sclerostin (22.5 kD), a powerful down regulator of bone metabolism, is produced in osteocytes and inhibits Wnt-coreceptor LRP5/6, a Wnt ligand.

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Patients with CKD are more likely to have coronary artery calcification (CAC) than those with normal kidney function.

The inflammatory pathway has an effect on the active process of CAC, which is linked to atherosclerosis.

Patients with chronic renal illness have been shown to have elevated levels of the serum sclerostin.

Serum sclerostin levels may be a good indicator of low-turnover bone disease in individuals with CKD, according to most recent investigations.[1]

In a nondialyzed CKD population, serum sclerostin levels have been linked to fatal and nonfatal cardiovascular events, according to a 2014 study by Kanbay and colleagues.

2. Patients and methods

This study was a case–control comparative study involving 30 CKD patients on regular hemodialysis in Al Hussein University Dialysis Unit, and 20 CKD patients with GFR less than 60 ml/min and 20 control group matched for age and sex with the previous two groups. Informed consents were obtained from all participants.

2.1. Exclusion criteria

Patients with a history of previous kidney transplantation, patients with atrial fibrillation, patients with severe comorbid conditions, and patients with a history of coronary graft surgery, coronary stent implantation, or valve surgery.

2.2. Methods

All patients were subjected to the following: full history, physical examination, laboratory investigations including estimation of GFR, complete blood count (CBC), lipid profile, total serum calcium, phosphorus, parathyroid hormone (PTH), and assessment of serum sclerostin level that was measured using ELISA immunoassay.

All patients received multi slice computed tomography (MSCT) scans using the 64-slice spiral computed tomography (CT) scanner. The degree of CAC scoring expressed in Agatston units.[2] Total CAC scores were calculated after summing the CAC scores of the left main artery, left anterior descending artery, left circumflex artery, and the right coronary artery.

2.3. Ethics and patient consent

For every operation that will be carried out, the patients' written informed permission has been acquired. All procedures flowed the Al-Azhar University Ethics Committee Regulation.

2.4. Statistical analysis

Version 24 of the Statistical Program for Social Sciences (SPSS) (IBM company, Chicago, USA) was utilized to analyze the data. Both qualitative and quantitative data were reported utilizing frequency and % for quantitative data. The mean (average) is the middle value in a collection of discrete numbers; it is the sum of values divided by the total number of values. The measure of a collection of values' dispersion is the SD. As opposed to a higher SD, which suggests that the results are dispersed across a greater range, a lower SD implies that the values tend to be close to the established mean. Data correlation was done using the Pearson's correlation coefficient (r) test.

3. Results

There is statistically significant higher CAC score (Agatston score) and calcified plaque in CKD patients on hemodialysis rather than those not on hemodialysis and those on hemodialysis more than

Table 1. Comparison of age and sex of the studied population.

	Dialysis ($N = 30$)	CKD ($N = 30$)	Control ($N = 20$)	f/χ^2	P value	Significance
Age (years)						
Range	22–73	35–62	22–56	1.991	0.145	NS
Mean ± SD	46.07 ± 13.80	46.25 ± 8.70	39.95 ± 10.90			
Sex [n (%)]						
Male	17 (56.7)	11 (55)	13 (65)	2.312	0.315	NS
Female	13 (43.3)	9 (45)	7 (35)			
Smoking [n (%)]						
No	22 (73.3)	14 (70)	20 (100)	7.083	0.029	S
Yes	8 (26.7)	6 (30)	0			

CKD, chronic kidney disease.

There is no statistically significant difference between CKD patients and controls as regards age and sex. Smoking was statistically significant higher in CKD patient than healthy controls.

Table 2. Comparison of the clinical data of the studied population.

	Dialysis ($N = 30$)	CKD ($N = 20$)	Control ($N = 20$)	f/χ^2	P value	Significance
BMI						
Range	20–28	21–34	21–35	5.011	0.009	HS
Mean ± SD	23.80 ± 1.97	25.40 ± 3.51	26.55 ± 3.86			
Systolic BP						
Range	110–170	110–175	100–140	23.658	<0.0001	HS
Mean ± SD	145.65 ± 14.27	148.33 ± 13.22	123.50 ± 11.71			
Diastolic BP						
Range	70–100	60–100	60–90	14.517	<0.0001	HS
Mean ± SD	90.00 ± 7.88	87.85 ± 9.91	77.00 ± 8.33			
eGFR						
Range	21–55	0 - <15	90–109	1331.4	<0.0001	HS
Mean ± SD	32.15 ± 9.15	15.00 ± 0.00	99.50 ± 5.92			
Anemia [*n* (%)]						
No	8 (26.7)	10 (50)	20 (100)	26.212	<0.0001	HS
Yes	22 (73.3)	10 (50)	0			

BP, blood pressure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.
There is statistically significant lower BMI and eGFR and higher systolic and diastolic blood pressure in CKD patients than healthy controls. Anemia was statistically significantly higher in CKD patients than healthy controls.

Table 3. Comparison of the laboratory data of the studied population.

	Dialysis ($N = 30$)	CKD ($N = 20$)	Control ($N = 20$)	f/χ^2	P value	Significance
Hemoglobin (g/dl)						
Range	6.5–14	8.5–11	11.8–16	49.72	<0.0001	HS
Mean ± SD	9.48 ± 1.84	10.07 ± 0.75	13.54 ± 1.34			
Calcium (mg/dl)						
Range	6.8–8.9	7.2–9	8.4–9.9	45.211	<0.0001	HS
Mean ± SD	7.93 ± 0.47	8.14 ± 0.42	9.14 ± 0.42			
Phosphorus (mg/dl)						
Range	3.2–6.2	4–6	3.3–4.8	39.773	<0.0001	HS
Mean ± SD	5.46 ± 0.69	5.30 ± 0.50	4.06 ± 0.39			
PTH (pg/ml)						
Range	270–1263	287–850	18–50	71.714	<0.0001	HS
Mean ± SD	663.93 ± 252.35	481.75 ± 148.65	32.50 ± 8.88			
Cholesterol (mg/dl)						
Range	150–250	140–240	100–176	40.018	<0.0001	HS
Mean ± SD	200.87 ± 24.62	194.35 ± 23.35	141.60 ± 23.92			
Triglyceride (mg/dl)						
Range	125–184	130–178	58–140	73.807	<0.0001	HS
Mean ± SD	158.23 ± 16.63	156.40 ± 15.25	100.40 ± 21.42			

CKD, chronic kidney disease.
There is statistically significant lower hemoglobin, calcium, and higher PTH, phosphorus cholesterol and TG in CKD patients than healthy controls especially those on hemodialysis.

Table 4. Comparison of serum sclerostin level of the studied population.

	Dialysis ($N = 30$)	CKD ($N = 20$)	Control ($N = 20$)	f/χ^2	P value	Significance
Sclerostin (ng/ml)						
Range	2.2–60.4	0.55–1.10	0.22–0.54	121.78	<0.0001	HS
Mean ± SD	1.88 ± 0.52	0.81 ± 0.16	0.36 ± 0.09			

CKD, chronic kidney disease.
There is statistically significant higher Sclerostin level in CKD patients than healthy controls especially in those on hemodialysis.

1 year than those less than 1 year. Also there is higher serum sclerostin level in CKD patients than healthy controls. Also, there is statistically significant association between positive MSCT scan for coronaries in CKD patients. Higher serum sclerostin levels were found in patients with CAC scoring (Agatston units) that shows coronary calcifications as follows (Tables 1–8 and Fig. 1).

Table 5. Comparison of the cardiac affection in chronic kidney disease patient dialysis more than 1 year and less than 1 year duration.

	<1 year ($N = 15$)	>1 year ($N = 15$)	t/χ^2	P value	Significance
CAC score (Agatston)					
Range	0–65	0–805	−4.277	0.001	HS
Mean ± SD	17.13 ± 24.34	281.27 ± 237.95			
CAC [*n* (%)]					
<1	6 (40)	2 (13.3)	2.727	0.099	NS
>1	9 (60)	13 (86.7)			
CAD [*n* (%)]					
No	6 (40)	2 (13.3)	0.689	0.497	NS
Minimal	5 (33.3)	0			
Mild	4 (26.7)	3 (20)	17.143	0.002	HS
Moderate	0	8 (53.3)			
Extensive	0	2 (13.3)			
Calcific plaque [*n* (%)]					
N	6 (40)	2 (13.3)	2.727	0.099	NS
Yes	9 (60)	13 (86.7)			

CAC, coronary artery calcification; CAD, coronary artery disease.
There is statistically significant higher CAC score (agatston) and calcificed plaque in chronic kidney disease patients on dialysis more than 1 year than those on dialysis less than 1 year.

Table 6. Comparison of the clinical data of chronic kidney disease patients on dialysis more than 1 year and less than a year duration.

	<1 year ($N = 15$)	>1 year ($N = 15$)	t/χ^2	P value	Significance
BMI					
Range	22–28	20–27	2.397	0.023	S
Mean ± SD	24.60 ± 1.76	23.00 ± 1.89			
Systolic BP					
Range	110–170	130–175	−0.824	0.417	NS
Mean ± SD	146.33 ± 14.20	150.33 ± 12.31			
Diastolic BP					
Range	70–100	70–100	0.689	0.497	NS
Mean ± SD	91.00 ± 7.84	89.00 ± 8.06			
Kt/V					
Range	0.9–2	0.6–1.4	2.638	0.013	HS
Mean ± SD	1.23 ± 0.33	0.97 ± 0.20			
Anemia [*n* (%)]					
1qq1	3 (20)	5 (33.3)	0.682	0.409	NS
Yes	12 (80)	10 (66.7)			

There is statistically significant lower BMI and Kt/V in end-stage renal disease patients on dialysis more than 1 year than those on dialysis less than a year.

Table 7. Comparison of serum sclerostin level between chronic kidney disease patients with and without dialysis.

	Dialysis ($N = 30$)	CKD ($N = 20$)	t	P value	Significance
Sclerostin (ng/ml)					
Range	0.60–2.80	0.55–1.10	10.575	<0.0001	HS
Mean ± SD	1.88 ± 0.52	0.81 ± 0.16			

CKD, chronic kidney disease.
There is statistically significant higher sclerostin level in CKD patients on hemodialysis than those not on hemodialysis.

Table 8. Comparison of serum scelorostin level in chronic kidney disease patients in relation to MSCT scan for coronaries.

	Positive MSCT scan ($N = 36$)	Negative MSCT scan ($N = 14$)	t	P value	Significance
Sclerostin (ng/ml)					
Range	0.60–2.80	0.55–1.90	2.993	0.005	HS
Mean ± SD	1.59 ± 0.70	1.10 ± 0.44			

There is statistically significant higher Sclerostin level in chronic kidney disease patients with positive than negative MSCT scan for coronaries.

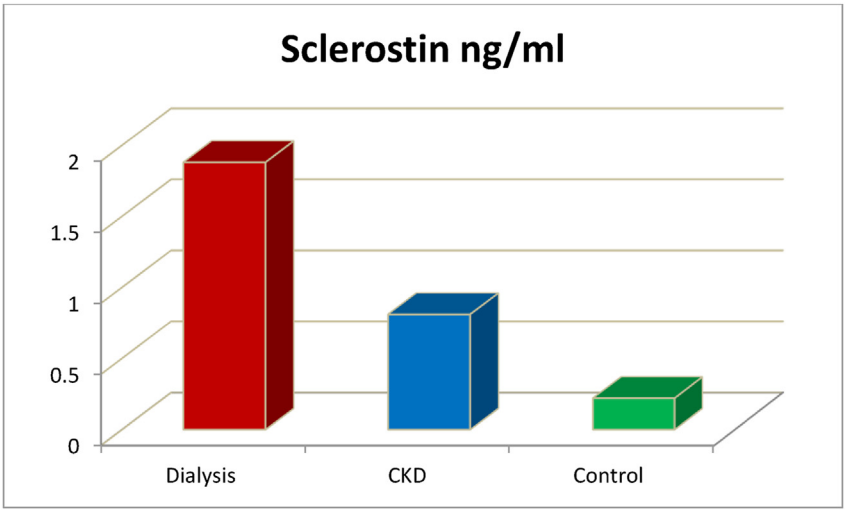

Fig. 1. Comparison of serum sclerostin level of the studied population.

4. Discussion

Chronic renal disease is becoming more common, and this trend is expected to continue.

Numerous risk factors, such as high blood pressure and type 2 diabetes, have been shown to hasten the course of CKD, ending in end-stage renal disease (ESRD).

Hemodialysis, peritoneal dialysis, and renal transplant are the mainstays of RRT for patients with ESRD.

By diffusion, convection, and ultrafiltration, hemodialysis substitutes the kidney's ability to remove waste from the bloodstream.

Serum sclerostin level was shown to be a possible biomarker for vascular calcifications in individuals with chronic renal disease in this case–control research.

To minimize the impact of analytical parameters on serum sclerostin levels, the ELISA immunoassay used in this investigation was the same as that utilized by Ishimura et al.[3] and Kanbay et al.[4]

Dialysis and nondialysis CKD patients, as well as the control group, all had substantially higher median levels of serum sclerostin.

Serum sclerostin levels rise in individuals with early stages of chronic renal disease, according to several studies.

In the context of the CKD–MBD disorder, the osteocyte responds to renal dysfunction by either decreasing excretion or increasing production, although the specific mechanism is still unclear.

This was in conformity with the findings of Gennari et al.[17] and Amrein et al.,[18] who observed that males had a higher serum sclerostin level than women.

Sclerostin was shown to have a strong connection with age and BMI among CKD patients.

In contrast to Gennari's results, however, the connection was less pronounced and was not important.

Age and other bone-metabolizing variables, such as parathyroid hormone, have an effect on the concentration of sclerostin, although we discovered a lot of regression in the relationship between GFR, sex, PTH, and serum phosphorus in patients with CKD.[7]

Sclerostin levels in CKD patients on hemodialysis were greater in those who were older than those who were younger in our research.

Dialysis and nondialysis patients had greater levels of serum sclerostin in men than in women, which was in keeping with previous research by Kanbay et al.,[8] which found that men had higher levels of serum sclerostin than women.

Serum sclerostin levels were shown to be significantly linked to both age and coronary calcification in our research.

Sclerostin is formed in the aortic valve tissue in the vicinity of sites of calcium accumulation, according to the findings of Brandenburg et al.,[9] who found an increase in the expression of the protein in calcium-calcified valves than in noncalcified valves.

Our investigation found a correlation between sclerostin levels and coronary calcification, which is consistent with the findings by Koos et al.[10]

He found significant correlation between serum sclerostin and vascular calcification. Serum sclerostin and calcification of the aorta were shown to have a substantial correlation, with high levels

predicting cardiovascular events in the early stages of CKD.

In CKD patients, we found a strong negative correlation between serum sclerostin levels and estimated glomerular filtration rate (eGFR).

With the findings of Morena et al.,[10] we may conclude that renal clearance may have a role in determining serum sclerostin levels, which is consistent with our findings.

Serum sclerostin was shown to be more sensitive than specific as a biomarker for coronary calcification in our investigation.

Cardiovascular calcification (CVD) affects the majority of dialysis users.

In HD patients, coronary calcification raises cardiovascular mortality and morbidity to alarming levels.

The average age of dialysis patients was 46.07 ± 13.80 years, while the average age of non-hemodialysis patients was 46.25 ± 8.70 years in the present research.

Serum Scl levels and vascular calcification levels in HD patients seemed to be linked; however, the patients in our study seemed to be younger than those in other studies.[9,11-13]

There has been an apparent rise in kidney transplantation among young people with ESRD in industrialized nations over the past decade as a result of improved ESRD screening and treatment measures for diabetes mellitus and hypertension.

Patients with CAC (>400) had substantially greater blood levels of sclerostin compared with those with CAC (100–400) and CAC (>100), according to ELISA data.

Patients with CAC (100) had the lowest sclerostin levels among the three groups studied.

Sclerostin overexpression was found to be associated with a greater risk of severe abdominal aortic calcification in regular HD patients in a previous study,[14] and research by Qureshi et al.[15] found that hemodialysis patients with greater coronary artery calcification had significantly higher serum levels of sclerostin as well.

When the Wnt signaling pathway is activated it helps the prevention and treatment of cardiovascular illnesses.

The Wnt signaling pathway is regulated by sclerostin as an inhibitor in the advancement of vascular calcification.[16]

For individuals with ESRD, the link between anemia and cardiovascular disease is well established.

When compared with other research, our patients' mean hemoglobin levels were much lower.[11,13,14]

Patients with hemophilia B may have worsening anemia as a result of environmental factors such as poor nutrition and a greater incidence of infectious illnesses in poorer nations.

Sex, diabetes mellitus, hypertension, and smoking had no influence on the blood level of Scl, according to our findings.

When looking at[12] research, Kanbay et al.[8] found that 60–86.7% of HD patients had calcifications in their coronaries, whereas Scl levels were shown to correlate with the degree of calcification.

According to Agatston,[2] we identified a correlation between sclerostin levels and CAC in our investigation, which supports Agatston's theory.

Also, CKD patients' blood sclerostin levels do not seem to be linked to their underlying causes.

Sclerostin levels were considerably greater in hemodialysis patients with CAC than in those who were not on HD.

Additional research is needed to determine if sclerostin is only a marker or a fundamental mediator of CAC and mortality in CKD patients.

In conclusion, we found that serum sclerostin may be a sensitive rather than a specific biomarker for coronary calcifications in those with CKD.

Sclerostin levels rise in patients with CKD.

Coronary calcification was shown to be associated with increased sclerostin growth.

Patients with CAC were older, had lower Kt/V, and longer dialysis experience, as well as a greater serum sclerostin level than those without the condition.

Conflict of interest

None declared.

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