Serum sclerostin levels in patients with non-dialysis chronic kidney disease

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Abstract

Objective: 1) To evaluate the serum sclerostin concentration in patients with CKD who have not yet undergone dialysis from stage G3 to G5, compared with a control group of healthy people with normal renal function. 2) To evaluate the relationship between serum sclerostin concentration and some related factors in patients with CKD. **Patients and methods:** This is a cross-sectional descriptive study on 84 patients with CKD who have not yet undergone dialysis (including 32 patients with stage 3, 4 CKD and 52 patients with stage 5 CKD) at the Department of Nephrology - Musculoskeletal, Hue Central Hospital and 60 healthy people with normal kidney function regularly came for health check-ups at the Internal Medicine Clinic of Hue University of Medicine and Pharmacy from April 2023 to 2025. **Results:** Our study was conducted on 84 non-dialyzed patients with chronic kidney disease (CKD) stages 3 to 5, including 32 patients in stages 3 and 4, and 52 patients in stage 5. The control group consisted of 60 healthy individuals with normal renal function. The mean serum sclerostin concentration in the control group was 359.52 ± 168.21 pg/mL. Serum sclerostin levels were significantly higher in the CKD group compared to controls ($p < 0.05$), with levels in the CKD stage 3–4 group recorded at 1090.63 ± 901.65 pg/mL and in the stage 5 group at 1464.26 ± 892.94 pg/mL. In our study, serum sclerostin levels were significantly higher in males than in females within the control group ($p < 0.05$) and in the CKD stage 5 group. Furthermore, serum sclerostin levels showed a statistically significant positive correlation with age in the CKD stage 3–4 group ($p < 0.05$). No statistically significant differences in serum sclerostin concentrations were observed between non-dialyzed CKD patients with or without hypertension or anemia. **Conclusion:** Sclerostin is a glycoprotein produced by osteocytes that inhibits bone formation through the Wnt/β-catenin signaling pathway. In patients with CKD, serum sclerostin levels progressively increase with advancing stages of the disease. Our study demonstrated that in non-dialyzed CKD stage 3 - 5 patients, serum sclerostin levels were significantly higher than in healthy controls with normal renal function. According to our findings, serum sclerostin concentrations were higher in males than in females in both the control group and in patients with CKD stage 5, and levels tended to increase with age. However, no statistically significant differences in serum sclerostin levels were observed between non-dialyzed CKD patients with or without hypertension or anemia.

Keywords: *Sclerostin, chronic kidney disease, CKD.*

1. BACKGROUND

Sclerostin is a glycoprotein secreted by osteocytes, functioning as an antagonist of the Wnt/β-catenin signaling pathway. It is considered a key regulator of bone mass. In humans, inhibition of sclerostin activity has been shown to significantly enhance bone formation [1]. The first clinical insights into the importance of sclerostin emerged from a deeper understanding of the pathophysiology of sclerosteosis and Van Buchem disease, a rare bone disease caused by loss-of-function mutations in the *SOST* gene, which encodes sclerostin. These conditions are characterized by markedly increased bone mass and excessive bone formation, providing compelling evidence of sclerostin's role in skeletal regulation [2]. Numerous studies have investigated serum sclerostin levels in various populations, particularly among patients with chronic kidney disease (CKD). Findings from numerous studies worldwide have demonstrated that patients with CKD have been consistently reported to exhibit higher serum sclerostin levels compared to healthy individuals. However, the exact role of sclerostin in CKD and its associations with various clinical factors remain incompletely understood. In Vietnam, no published studies to date have examined serum sclerostin concentrations in CKD patients, especially in those not yet receiving dialysis, nor explored its relationship with CKD-related parameters. Therefore, we conducted the study entitled "Serum Sclerostin Levels in Patients with Non-Dialysis Chronic Kidney Disease" with the following objectives:

1. To evaluate serum sclerostin levels in non-dialysis chronic kidney disease (CKD) patients from stage 3 to stage 5, in comparison with a control group of healthy individuals with normal kidney function.

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2. To assess the association between serum sclerostin levels and various chronic kidney disease-related factors in non-dialysis CKD patients.

2. MATERIALS AND METHODS

2.1. Study subjects

- Study period and location: Our study was conducted at the Department of Nephrology – Rheumatology, Hue Central Hospital, and the Internal Medicine Clinic of Hue University of Medicine and Pharmacy Hospital from April 2023 to 2025.

- Inclusion criteria:

+ Patient group: Patients aged ≥ 16 years who meet the diagnostic criteria for chronic kidney disease (CKD) stages based on the 2012 KDIGO guidelines using estimated glomerular filtration rate (eGFR) (see table below), and who consent to participate in the study [3].

Grade	eGFR (ml/min/1.73m^2)
G1	> 90
G2	60 - 89
G3a	45 - 59
G3b	30 - 44
G4	15 - 29
G5	< 15

+ Control group: 60 healthy adult individuals with normal kidney function undergoing routine health check-ups at the Internal Medicine Clinic of Hue University of Medicine and Pharmacy Hospital.

- Exclusion criteria: Patients who do not consent to participate in the study. Patients were excluded if they met any of the following conditions: Acute kidney injury or acute exacerbation of chronic kidney disease; critical or life-threatening condition precluding participation in the study; use of any medications known to affect bone turnover, including calcium or vitamin D supplements, anti-osteoporotic agents (e.g., bisphosphonates, raloxifene), corticosteroids, calcimimetics, or other drugs influencing parathyroid hormone (PTH) levels within at least one month prior to enrollment; presence of severe active infection; neuropsychiatric disorders impairing cognition or the ability to provide informed consent.

2.2. Research method

- Study design: Cross-sectional descriptive study.

- Sample size and sampling method: Convenience sampling was used to enroll all eligible patients diagnosed with chronic kidney disease (CKD) at various stages (stage 3 - 5) who were admitted for inpatient treatment during the study period. The study included 84 CKD patients, comprising 32 patients at stages 3 and 4 (G3-4 group) and 52 patients at end-stage CKD not yet on dialysis (G5ND group). The control group consisted of 60 healthy individuals with normal kidney function undergoing routine health check-ups.

- Clinical variable : Sex, age, and blood pressure. Diagnosis of hypertension (HTN): Patients were diagnosed with hypertension if systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg (4).

- Paraclinical variables in the CKD patient group:

+ Complete Blood Count: Hemoglobin (HGB). Anemia diagnosis according to KDIGO 2012: Anemia in adult or pediatric patients over 15 years old with chronic kidney disease is defined as hemoglobin (Hb) levels below 13 g/dL in males and below 12 g/dL in females (3).

+ Biochemical parameters: Urea, creatinine. Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI 2009 equation.

+ Serum sclerostin quantification was performed using a sandwich ELISA method, with the assay kit manufactured by Abbexa, United Kingdom.

2.3. Data analysis

Using SPSS version 27.0 software. Percentage calculations, mean values, and statistical tests were applied. A p-value < 0.05 was considered statistically significant.

2.4. Ethical Considerations in Medical Research

The study was approved by the Ethics Committee of Hue University of Medicine and Pharmacy prior to implementation (Ethical approval No. H2023/045, approved on May 5, 2023). All participants were fully informed of the study objectives and procedures and received detailed explanations regarding the voluntary nature of their participation.

3. RESULTS

Table 1. General Characteristics of the Study Population

Characteristics	Control group [1] (n = 60)	G3-4[2] (n = 32)	G5ND[3] (n = 52)	p
Age	49.27 ± 10.98	52.66 ± 22.97	50.85 ± 18.68	$p^{1\&2}$ = 0.358; $p^{1\&3}$ = 0.605

Gender (Male/Female)	25/35	16/16	27/25	
SBP (mmHg)	115.42 ± 10.35	142.19 ± 23.52	149.04 ± 17.29	**$p^{1\&2} < 0.001$; $p^{1\&3} < 0.001$**
DBP (mmHg)	68.58 ± 6.83	82.50 ± 10.16	82.88 ± 14.73	**$p^{1\&2} < 0.001$; $p^{1\&3} < 0.001$**
HTN (%)	0%	53.13%	82.69%	
HGB (g/dl)		10.253 ± 1.740	8.390 ± 1.573	**$p^{2\&3} < 0.001$**
Anemia (%)		88%	100%	**$p^{2\&3} = 0.009$**
Urea (mmol/l)	4.64 ± 1.09	14.23 ± 8.31	31.02 ± 12.61	**$p^{1\&2} < 0.001$; $p^{1\&3} < 0.001$**
Creatinine (µmol/l)	67.62 ± 12.19	196.53 ± 68.48	855.45 ± 420.54	**$p^{1\&2} < 0.001$; $p^{1\&3} < 0.001$**
eGFR (ml/min/1,73m²)	99.72 ± 10.68	32.66 ± 12.55	6.44 ± 4.02	**$p^{1\&2} < 0.001$; $p^{1\&3} < 0.001$**

+ The mean age of the control group was 49.27 ± 10.98 years; the CKD stage 3-4 group was 52.66 ± 22.97 years, and the CKD stage 5 non-dialysis (G5ND) group was 50.85 ± 18.68 years. There was no statistically significant difference in age between the control group and each CKD patient group.

+ Regarding gender distribution, the control group had a male/female ratio of 25/35, the G3-4 group had 16/16, and the G5ND group had 27/25.

+ Both systolic blood pressure (SBP) and diastolic blood pressure (DBP) were significantly higher in the CKD groups compared to the control group ($p < 0.001$). No hypertension cases were observed in the control group, whereas more than 80% of CKD patients in the G5ND stage had hypertension, and over half of the G3-4 group were diagnosed with hypertension.

+ The mean hemoglobin (HGB) concentration in the G3-4 group decreased with disease progression compared to the G5ND group, showing statistical significance ($p < 0.05$). Nearly 90% of the G3-4 group were anemic, while all patients in the stage 5 group had anemia.

+ The mean blood urea nitrogen (BUN) and serum creatinine levels were significantly higher in the CKD groups compared to controls ($p < 0.05$), and the estimated glomerular filtration rate (eGFR) was significantly lower in CKD patients compared to controls ($p < 0.05$).

Table 2. Serum Sclerostin levels in CKD patients and control group

	Control group [1] (n = 60)	**G3-4[2] (n = 32)**	**G5ND[3] (n = 52)**
Sclerostin (pg/ml)	359.52 ± 168.21	1090,63 ± 901,65	1464,26 ± 892,94
$p^{1\&2} < 0.01$; $p^{1\&3} < 0.01$			

The mean serum sclerostin concentration in the control group of our study was 359.52 ± 168.21 pg/mL. The CKD groups exhibited significantly higher serum sclerostin levels compared to the control group ($p < 0.05$); specifically, the mean concentrations were 1090.63 ± 901.65 pg/mL in the G3-4 group and 1464.26 ± 892.94 pg/mL in the G5ND group.

Table 3. Serum Sclerosin levels in relation to some factors in the study population

	Characteristics		**Control group [1] (n = 60)**	**G3-4[2] (n = 32)**	**G5ND[3] (n = 52)**
Sclerostin (pg/ml)	**Gender**	Male	421.61 ± 195.49	838.15 ± 520.90	1616.21 ± 900.85
		Female	315.16 ± 131.38	1343.11 ± 1128.18	1300.14 ± 872.46
		p	**p = 0.014**	p = 0.291 (test Mann Whitney)	p = 0.172 (test Mann Whitney)

Sclerostin (pg/ml)	Age group	< 40	327.09 ± 127.00	525.11 ± 525.87	1284.98 ± 826.27
		40-60	352.33 ± 179.59	1307.96 ± 915.52	1557.17 ± 763.79
		> 60	424.03 ± 184.47	1435.40 ± 962.99	1560.95 ± 1068.89
		p	p = 0.298	**p = 0.020 (test Kruskal Wallis)**	p = 0.717 (test Kruskal Wallis)
	HPN	Yes		1161.69 ± 1045.06	1754.66 ± 936.59
		No		1027.93 ± 781.39	1403.47 ± 882.76
		p		p = 0.985	p = 0.346
	Anemia	Yes		1520.20 ± 1477.98	
		No		1029.26 ± 812.06	1464.26 ± 892.94
		p		p = 0.608	

In the control group. serum sclerostin levels were significantly higher in males compared to females ($p < 0.05$). Similarly, in the CKD G5ND group, males also exhibited higher sclerostin levels than females. However, in the G3-4 group, females showed higher sclerostin levels than males, though these differences were not statistically significant ($p > 0.05$). Serum sclerostin concentrations tended to increase with age in both the control and CKD groups, with the difference reaching statistical significance in the CKD G3-4 group ($p < 0.05$). Among CKD patients, serum sclerostin levels were higher in the non-hypertensive group compared to the hypertensive group, but this difference was not statistically significant. In the G3-4 group, sclerostin levels were higher in patients without anemia (1520.20 ± 1477.98 pg/mL) compared to those with anemia (1029.26 ± 812.06 pg/mL); however, this difference was not statistically significant ($p > 0.05$).

4. DICUSSION

Our study was conducted on 84 patients with chronic kidney disease (CKD) from stage 3 to stage 5 who had not yet undergone dialysis, including 32 patients in stages 3 and 4, and 52 patients in stage 5. The control group consisted of 60 healthy individuals with normal renal function. The age distribution between the control group and CKD patients was comparable. Regarding gender distribution, the male-to-female ratio was 25/35 in the control group, 16/16 in the G3-4 group, and 27/25 in the G5ND group. The mean blood urea nitrogen and serum creatinine levels were significantly higher in the CKD groups compared to the control group ($p < 0.05$), while the estimated glomerular filtration rate (eGFR) was significantly lower in the CKD groups ($p < 0.05$). The mean serum sclerostin level in the control group was 359.52 ± 168.21 pg/mL. CKD patients demonstrated significantly higher serum sclerostin concentrations than the control group ($p < 0.05$). Specifically, mean sclerostin levels were 1090.63 ± 901.65 pg/mL in the G3-4 group and 1464.26 ± 892.94 pg/mL in the G5ND group.

In the control group, our study included 60 individuals with a mean age of 49.27 ± 10.98 years. The mean serum sclerostin concentration was 359.52 ± 168.21 pg/mL, equivalent to 15.819 ± 7.401 pmol/L. Several international studies investigating serum sclerostin levels in patients with CKD have also included control groups, with varying results. For example, the study by Mehmet Kanbay included a control group of 47 individuals with a median age of 49.0 (47.0 - 59.0) years. In that study, the median serum sclerostin level was reported as 52.0 (49.0 - 54.9) pmol/L, measured using an ELISA kit provided by BioMedica [5]. In the study conducted by Emad Abdallah, the control group consisted of 20 individuals with a mean age of 50.6 ± 15.20 years. The mean serum sclerostin concentration in this group was 29.38 ± 0.84 pmol/L, measured using an ELISA kit from R&D Systems [6]. The differences in serum sclerostin concentrations observed among control groups across various studies may be attributed to the use of different commercial ELISA kits from various manufacturers. A study by Isabelle Piec and colleagues in 2016 compared serum and EDTA plasma sclerostin levels measured using three different commercial ELISA kits-Biomedica, TECOmedical, and R&D Systems - in a group of healthy individuals aged 18 to 26 years [7]. The results of the study showed that serum and EDTA plasma sclerostin concentrations were highest when measured using the Biomedica kit (35.5 ± 1.1 pmol/L and 39.4 ± 2.0 pmol/L, respectively), followed by the TECOmedical kit (21.8 ± 0.7 pmol/L and 27.2 ±

1.3 pmol/L), and lowest with the R&D Systems kit (7.6 ± 0.3 pmol/L and 30.9 ± 1.5 pmol/L). Similarly, another study by Annelies De Maré and colleagues, which concurrently assessed sclerostin levels using multiple commercial ELISA kits, confirmed this variability in measured concentrations depending on the assay used [8]. This is an important finding that should be taken into account when interpreting data from different studies utilizing various assay methods. Although there are differences in the absolute values of serum sclerostin concentrations measured using four different assays, the results from all four tests showed significant correlations with sclerostin expression in bone tissue. Moreover, serum sclerostin levels measured by different assays also demonstrated good inter-assay correlation.

In the CKD patient group, the mean serum sclerostin concentration was 1090.63 ± 901.65 pg/mL (47.99 ± 39.67 pmol/L) in the G3-4 group and 1464.26 ± 892.94 pg/mL (64.43 ± 39.29 pmol/L) in the G5ND group, both significantly higher than that of the control group, which was 359.52 ± 168.21 pg/mL (15.82 ± 7.40 pmol/L) ($p < 0.05$). Furthermore, serum sclerostin levels in the G5ND group were significantly higher than in the G3-4 group. A study by Solenne Pelletier involving 90 CKD patients ranging from stage 1 to stage 5, with a mean eGFR of 66.5 mL/min/1.73m², reported a median serum sclerostin level of 53.5 (37.5 - 77.2) pmol/L. In this study, sclerostin concentrations were higher in patients with eGFR < 60 mL/min/1.73m² and were highest among those with end-stage renal disease (ESRD) [9]. According to Pelletier et al., elevated serum sclerostin levels begin to appear from CKD stage 3. This study also reported that serum sclerostin concentrations in pre-dialysis end-stage CKD patients were approximately four times higher than those in the control group with normal renal function. Similarly, the study by Mehmet Kanbay, which included 173 pre-dialysis CKD patients from stages 3 to 5, also demonstrated that serum sclerostin levels were significantly higher in CKD patients compared to the control group (63.5 pmol/L vs. 52.0 pmol/L, $p < 0.001$), with a mean difference of 17.7 pmol/L (95% CI: 13.9 - 21.4 pmol/L) [5]. This study also reported a statistically significant stepwise increase in serum sclerostin levels across CKD stages. Specifically, patients with CKD stage 3 had higher serum sclerostin levels than the control group ($p < 0.001$), stage 4 patients had higher levels than those in stage 3 ($p = 0.02$), and stage 5 patients had higher levels than stage 4 ($p = 0.001$). There remains some controversy regarding the mechanisms underlying elevated serum sclerostin concentrations in CKD patients. Daniel Cejka suggested that the rise in serum sclerostin in CKD is not primarily due to reduced renal clearance. On the contrary, sclerostin elimination through the kidneys may actually increase as renal function declines [10]. Furthermore, increased extra-skeletal production of sclerostin may be one of the contributing factors to the elevated serum sclerostin levels. Roforth and colleagues reported that bone mRNA expression of sclerostin does not increase in elderly individuals despite elevated serum sclerostin concentrations [11]. Another animal study by Sabbagh et al. suggested that increased production by osteocytes may be the primary factor contributing to elevated serum sclerostin levels in patients with chronic kidney disease [12]. Data from this study concluded that renal osteodystrophy occurs early in the progression of chronic kidney disease and demonstrated inhibition of the β-catenin signaling pathway in bone cells. The study also showed that alterations in the RANK/OPG ratio related to β-catenin occur even before changes in parathyroid hormone (PTH) levels are detected. This highlights the complexity of bone-related changes during the progression of CKD and underscores the necessity for further research to optimize therapeutic strategies for bone and mineral disorders in these patients. Overall, our findings, together with international studies, confirm that serum sclerostin levels are significantly elevated in CKD patients, likely due to multiple mechanisms. However, variability in assay methods and pathological factors complicates direct comparison of results across studies. Standardization of assay techniques, sample handling, storage conditions, and timing of analysis is essential to improve consistency and reliability in future research.

Regarding the association between serum sclerostin levels and certain chronic kidney disease-related factors in pre-dialysis CKD patients, our study found that in the control group, serum sclerostin concentrations were significantly higher in males compared to females ($p < 0.05$). Similarly, in the CKD G5ND group, sclerostin levels were higher in males than females. However, in the G3-4 group, females exhibited higher sclerostin concentrations than males, although these differences were not statistically significant ($p > 0.05$). Several studies investigating the influence of sex on serum sclerostin levels across different populations have reported findings consistent with our control group results. For instance, the study by Ulrike I. Modder assessing

the roles of sex, age, and bone mass on sclerostin levels found that males had significantly higher serum sclerostin concentrations than females [13]. To explain the differences in serum sclerostin levels according to sex, previous studies have demonstrated that estrogen, rather than testosterone, reduces circulating sclerostin concentrations. Higher estrogen levels in post-pubertal girls lead to lower sclerostin levels, which tend to be maintained throughout adulthood [14]. The serum sclerostin levels in the control group of our study showed results consistent with those reported in previous studies. However, in the CKD G3-4 patient group, the sex-related differences were not statistically significant; this may be explained by the fact that, in CKD patients, variations in serum sclerostin levels more likely reflect the indirect effects of disease severity rather than a direct influence of sex. Serum sclerostin levels in both the overall CKD patient group and the control group showed an increasing trend with age, particularly in the G3-4 group, where the gradual increase in serum sclerostin levels was statistically significant ($p < 0.05$). Numerous studies in healthy populations have demonstrated that serum sclerostin concentrations increase with age in both adults and adolescents [15]. According to Kirmani et al., serum sclerostin levels peak at approximately 10 years of age in females and 14 years of age in males, followed by a gradual decline during late puberty until reaching the lowest levels at the end of puberty. Subsequently, sclerostin levels increase progressively throughout the remainder of adulthood [14]. The increase in serum sclerostin levels with aging in elderly individuals suggests that elevated sclerostin production may contribute to the age-related decline in bone formation. However, despite the observed rise in serum sclerostin with age, the study by Matthew M. Roforth et al. found that aging was not associated with increased sclerostin mRNA expression in bone tissue [11]. In both the control group and the CKD stage 5 non-dialysis (G5ND) group, although serum sclerostin levels tended to increase with age, these differences were not statistically significant ($p > 0.05$). This may be due to limited sample size or confounding factors such as the degree of renal function decline and comorbidities. Regarding the association between serum sclerostin levels and the presence or absence of hypertension subgroups, our study found no statistically significant difference in sclerostin concentrations between these groups in CKD patients. Sclerostin is an endogenous inhibitor of the Wnt/β-catenin signaling pathway and has been shown to be associated with cardiovascular damage in adults. According to the study by Piotr Skrzypczyk et al., sclerostin levels did not correlate with non-invasive arterial damage indices but were inversely related to systolic blood pressure [16]. However, further clinical studies are needed to elucidate the relationship between hypertension and sclerostin, as well as the role of the Wnt/β-catenin signaling pathway in cardiovascular systems, particularly in patients with chronic kidney disease (CKD). Regarding the association between serum sclerostin levels and the presence or absence of anemia subgroups, our study found no statistically significant difference in sclerostin concentrations between these groups in CKD stage 3 - 4 patients (all patients in the G5ND group had anemia). The study by Mahmoud et al. demonstrated an inverse correlation between serum sclerostin levels and hemoglobin concentrations [17]. Although both elevated serum sclerostin levels and anemia have been demonstrated to be common and associated with adverse outcomes in patients with chronic kidney disease (CKD), current research primarily focuses on the role of sclerostin in bone metabolism and vascular calcification. Deeper investigations into the effects of sclerostin on the mechanisms of anemia in CKD patients remain lacking and warrant further study.

5. CONCLUSIONS

Sclerostin is a glycoprotein produced by osteocytes that functions as an inhibitor of bone formation through the Wnt/β-catenin signaling pathway. In patients with chronic kidney disease (CKD), serum sclerostin levels increase progressively across the stages of CKD. Our study demonstrated that in CKD patients at stage 3 to 5 who have not yet undergone dialysis, serum sclerostin levels were significantly higher compared to healthy controls with normal renal function. According to our findings, serum sclerostin levels were higher in males than females in both the control group and the stage 5 CKD group, and serum sclerostin levels tended to increase with age. However, our study did not find statistically significant differences in serum sclerostin levels between CKD patients not on dialysis with or without hypertension or anemia.

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