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The relationship between plasma sclerostin level to various nutritional factors in hemodialysis diabetic and non-diabetic patients

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Abstract

Introduction: Sclerostin is a glycoprotein secreted by osteocytes and has anti-anabolic properties. High sclerostin levels in cases with chronic renal disease are associated with an increased risk of mineral and bone metabolism disorders.

Objectives: The aim of this study was to determine the correlation between serum sclerostin levels and nutritional factors, anemia severity and dialysis adequacy in end-stage renal disease (ESRD) on maintenance hemodialysis.

Patients and Methods: This descriptive-analytic study was conducted on 89 diabetic and non-diabetic hemodialysis individuals. The data including age, gender, body mass index (BMI), duration of the disease was extracted from patients' records. The dialysis adequacy was determined using the urea reduction ratio (URR) and Kt/V indices. Blood samples were collected to determine the levels of calcium, phosphorus, albumin, intact parathyroid hormone and sclerostin.

Results: According to the results, mean parathyroid hormone and duration of chronic renal failure were higher in the non-diabetics than those in the diabetic population ($P<0.05$). In non-diabetic patients, serum sclerostin had a negative correlation with plasma hemoglobin, calcium, serum phosphate and BMI. Serum sclerostin also had a positive correlation with URR and Kt/V. In diabetic patients, sclerostin had a negative correlation with plasma hemoglobin and parathyroid hormone, which was significant with hemoglobin (r=-0.343, $P=0.021$). Furthermore, in diabetic patients, sclerostin had a positive relationship with BMI, URR and Kt/V, which was significant with URR (r=0.463, $P=0.001$).

Conclusion: The results showed the correlation of sclerostin with various biochemical and nutritional factors, however our results requites further investigation by larger studies.

Keywords: Sclerostin, Chronic renal disease, End stage renal failure, Dialysis adequacy, Body mass index, Glomerular filtration rate, diabetes, Parathyroid hormone, Hemodialysis

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Introduction

Chronic kidney disease (CKD) is a growing public health problem worldwide that results in end-stage renal failure (1). CKD is a common disorder with a variable clinical course and is related to increased mortality (2). Affected patients require dialysis or kidney transplantation (3). In hemodialysis, blood is filtered outside the patient's body using an artificial kidney (4,5). Renal osteodystrophy is a common problem for people with CKD, since the risk of fracture in dialysis patients is 2–14 times higher compared to the general population (6,7). The CKD–mineral and bone disorder (CKD–MBD) syndrome is an important complication of kidney diseases (8). Management of CKD-MBD requires the evaluation of bone metabolism factors comprising parathyroid hormone, calcium, phosphorus, vitamin D3 and other involved factors (8,9). High phosphate level leads to several complications, including secondary hyperparathyroidism, renal osteodystrophy, cardiovascular disease and progression of chronic renal failure (10). Vitamin D ameliorates secondary hyperparathyroidism and has therapeutic effects on the renal osteodystrophy (11, 12). Among the factors affecting the metabolism of bones, sclerostin is the most important one, which has recently been discovered and studied (13). This glycoprotein factor has anti-anabolic effects that decreases the osteoblast differentiation by inhibiting the Wnt/β-catenin signaling pathway, thereby increases the risk of bone fractures (14). The serum level of sclerostin increases with age, in both men and women and also decreases with the intermittent estrogen treatment or parathyroid hormone therapy (9-14). Parathyroid disorders can manifest their regulatory effects because of the parathyroid hormone (PTH; parathormone) impact on serum sclerostin levels. The evidence shows that

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Implication for health policy/practice/research/ medical education

In a study on 89 diabetic and non-diabetic hemodialysis patients, we found serum sclerostin had a positive correlation with urea reduction ratio (URR) in diabetic population.

patients with primary hyperparathyroidism had decreased sclerostin levels and those with hypoparathyroidism had increased sclerostin levels. Recent data suggests that the higher serum sclerostin levels are associated with increased fracture rates (13). It has been reported that, high serum sclerostin levels are associated with some variables including age, male gender, diabetes mellitus (DM), high bone mineral density, low-bone regeneration rate, lowered glomerular filtration rate, decreased activity of parathyroid hormone (PTH) and serum alkaline phosphatase (13, 14). Recent clinical studies demonstrated that treatment with anti-sclerostin antibodies could improve the bone quality. Furthermore, serum sclerostin levels in chronic renal disease cases were found to increase compared with the general population (11, 12). Sclerostin also is a potent inhibitor of osteoblastogenesis (15).

Objectives

Numerous studies have shown that circulating sclerostin levels increase with the severity of CKD and is associated with bone formation problems and abnormalities. Given the inverse relationship between PTH and sclerostin levels, the present study aimed to investigate the relationship between serum sclerostin level as a risk factor with other harmful factors affecting morbidity and mortality in patients undergoing dialysis such as body mass index (BMI), serum albumin, dialysis quality and anemia.

Patients and Methods

Study population

This descriptive-analytic study was conducted on 89 diabetic and non-diabetic hemodialysis individuals hospitalized in dialysis department of Hajar hospital in Shahrekord, Iran, employing the sampling method. Out of 89 patients, 44 (49.4%) were non-diabetic and 45 (50.6%) diabetics. In addition, 34 (38.2%) were female, 55 (61.8%) were male. Prior to commencing the study, ethical clearance was sought from the medical ethics committee and written informed consent was obtained from all study patients. The data used for this study including age, gender, (BMI and duration of the disease were extracted from patient's records. BMI was calculated as weight in kg divided by the square of height in meters. The adequacy of dialysis was calculated based on Kt/V formula. Additionally, blood samples were drawn after a 12-hour overnight fast for biochemical tests including calcium, phosphorus, albumin, PTH and sclerostin levels. The sclerostin serum concentration were measured by enzyme-linked immunosorbent assay (ELISA) method using the kits provided from Tarvand Sina company.

Statistical analysis

Correlation analysis was conducted to determine the relationship between sclerostin level and nutritional factors, anemia and dialysis adequacy. One-way analysis of variance (ANOVA), chi-square and t test were conducted to compare the groups. The data were analyzed by Stata software. A P value of <0.05 was considered as statistically significant.

Results

A total of 89 patients included in this investigation. The comparison of age, blood biochemical factors, duration of chronic renal failure, dialysis duration and adequacy and also BMI variables shown in Table 1.

The results of this study revealed a significant difference between age ($P=0.005$), BMI ($P<0.001$) and duration of chronic renal disease ($P=0.001$) in both diabetic and non-diabetic groups. The mean age in the diabetic group

Table 1. Comparison of the variables studied between diabetic and non-diabetic groups

Variable (mean ± standard deviation)	Studied groups		*P* value
	Diabetic	Non-diabetic	
Age (y)	96.43 ± 67.10	59.17±7.43	0.005*
Sclerostin (ρmol/L)	88.97 ± 54.96	97.11 ± 87.64	0.685
Kt/V (mL/min)	27.12 ± 1	28.13 ± 1	0.720
Urea reduction ratio (%)	65.05 ± 0.0	65.03 ± 0.0	0.440
Body mass index (kg/m^2)	84.67 ± 25.3	89.21 ± 21.4	0.000*
Hemoglobin (g/dL)	22.10 ± 10.1	1332.57 ± 10.1	0.737
Albumin (g/dL)	19.79 ± 4.00	8.84 ± 4.00	0.557
Calcium (mg/dL)	76.62 ± 8.00	69.54 ± 8.00	0.579
Phosphorus (mg/dL)	9.80 ± 5.00	80.87 ± 4.00	0.112
PTH (ρg/mL)	348.24 ± 19.28	693.853 ± 60.05	0.011*
Duration of chronic renal failure (mon)	28.27± 84.60	65.66 ± 95.67	0.001*
Duration of dialysis (mon)	62.38 ± 11.1	26.68 ± 11.1	0.264

* A significant difference was set at the level of $P<0.05$ in both diabetic and non-diabetic groups.

Table 2. Correlation between sclerostin and other variables in diabetic and non-diabetic groups

Variables	Studied groups	
	Diabetics *P* value (r)	Non-diabetics *P* value (r)
Age (year)	0.22 (-0.18)	≤0.001 (-0.52)*
Calcium (mg/dL)	0.560 (-0.089)	0.446 (-0.118)
Phosphorus (mg/dL)	0.038 (0.810)	0.051 (-0.296)
Kt /V (mL/min)	0.457 (0.114)	0.092 (0.275)
Urea reduction ratio (%)	0.001 (0.462)*	0.463 (0.121)
Hemoglobin (g/dL)	0.021 (-0.343)*	0.359 (-0.142)
Albumin (g/dL)	0.700 (-0.059)	0.965 (0.007)
PTH (ρmol/L)	0.911 (-0.17)	0.742 (0.051)
Duration of dialysis (mon)	0.8 (0.038)	0.62 (0.076)
Duration of CKD (mon)	0.26 (0.17)	0.122 (0.38)*
BMI (kg/m^2)	0.484 (0.107)	0.181 (-0.205)

* A significant difference at the level of $P < 0.05$ in both diabetic and non-diabetic groups.

was greater than the non-diabetic group. Table 2 shows the correlation between sclerostin and some biochemical variables, the duration of chronic renal failure, the duration of dialysis and the efficacy of hemodialysis and also BMI.

In non-diabetic patients, serum sclerostin was negatively correlated with age, hemoglobin, BMI, serum calcium and phosphate levels, although they were non-significant. In non-diabetic patients also serum sclerostin had a positive correlation with URR and Kt/V indices, which was statistically significant ($P<0.001$, $r=52$). There was also a positive association between the duration of chronic renal disease and serum sclerostin in this group, however it was not significant ($P=0.122$, $r=0.38$). A negative association was also found between serum sclerostin level and plasma hemoglobin concentration, age and serum calcium in diabetic patients. We also found a significant negative relationship of sclerostin with plasma hemoglobin level ($P=0.021$, $r=-0.34$). Moreover, there was a positive significant relationship between the duration of chronic renal disease with dialysis adequacy as URR ($P=0.001$, r = 0.462) and Kt/V indices in diabetic patients.

Table 3. Frequency and percentage of calcium carbonate and calcitriol intake in patients

Drugs administered for patients	Users No. (%)	Non-users No. (%)
Calcium carbonate	14 (15.7)	75(84.3)
Calcitriol	68 (76.4)	21(23.6)

Frequency and percentage of calcium carbonate and calcitriol intake in patients have been represented in Table 3. According to Table 4, no significant difference was shown in both diabetic and non-diabetic patients in terms of frequency and sevelamer administration.

The results of our study showed no significant difference between the levels of PTH and sclerostin in terms of sevelamer intake; however, it was low in patients who took sevelamer three times per day (Table 5).

Discussion

According to the results, BMI was significantly higher in the diabetic group than in the non-diabetic group. In addition, the current study found that PTH levels in non-diabetic group was significantly higher than the diabetic group, which could be attributed to the prolonged duration of chronic renal failure in these patients. Sclerostin is a glycoprotein secreted by osteocytes and has anti-anabolic properties, as well as regulates bone metabolism. Sclerostin plays a critical role in the inhibition of Wnt signaling pathway. Sclerostin together with Dickkopf1 (Dkk1), can bind to LRP5 and LRP6 receptors inhibiting Wnt signaling pathway in bone marrow cells, which in turn reduces the proliferation, differentiation and longevity of osteosynthetic cells (16-20). Findings from several animal models support the role of sclerostin as a bone suppressor in genetically engineered mice. These findings suggested that lack of sclerostin increased bone strength in genetically engineered mice (21,22). In addition, the results of clinical studies have shown that low sclerostin level and high level of Wnt signaling increase bone mineral density and formation. However, low level of Wnt signaling leads to diminished bone density and formation (23). The evidence from this study suggests that serum sclerostin levels in non-diabetic patients were significantly higher than diabetic patients, however it was not significant.

This finding does not corroborate the idea of Viaene et al who suggested a positive relationship between presence of diabetes and serum levels of sclerostin in hemodialysis patients (15). High serum sclerostin levels in non-diabetic patients may be due to the prolonged duration of chronic renal failure in these patients compared to diabetic hemodialysis patients. This finding is consistent with those findings of Pelletier et al, who reported that serum sclerostin level in patients with estimated glomerular filtration rate (eGFR) less than 60 mL/min is higher other patients, which is frequently observed in end-stage renal

Table 4. Frequency and percentage of sevelamer administration in both diabetic and non-diabetic patients

Patients	Number of sevelamer administration per day				P value
	No use No. (%)	One tablet per day No. (%)	Two tablets per day No. (%)	Three tablets per day No. (%)	
Non-diabetics	38 (86.4)	1 (2.3)	4 (9.1)	1 (2.3)	0.69
Diabetics	38 (84.4)	2 (4.4)	5 (11.1)	0 (0)	

Table 5. Average sclerostin and serum parathyroid hormone levels in terms of the Renagel use per day

Variable	Mean ± standard deviation	Number of patients	Number of Renagel use per day	*P* value
Sclerostin (ρmol/L)	90.104 ± 49.44	79	No use	0.882
	128.141 ± 30.80	3	One tablet per day	
	110.137 ± 75.013	9	Two tablets per day	
	31.0 ± 30.00	1	Three tablets per day	
	93.107 ± 15.62	89	Total	
PTH (pg/mL)	472.597 ± 21.13	76	No use	0.079
	1391.1421 ± 36.15	3	One tablet per day	
	655.612 ± 50.30	9	Two tablets per day	
	135.00 ± 50.00	1	Three tablets per day	
	518.644 ± 95.65	89	Total	

disease (ESRD) patients (14). In fact, serum sclerostin levels increase with the progression of CKD in non-diabetic patients (14,24), resulting in the long-term risk of CKD. Numerous investigations indicate that patients with type 2 DM and chronic renal failure tended to have a higher sclerostin levels, which is associated with weak and fragile bone mineral density and the increased risk of fracture in these patients (18,21-23,25).

The results of the current study indicated a negative relationship between serum calcium and phosphate with serum sclerostin in non-diabetic hemodialysis patients although they were not significant. Additionally, serum sclerostin levels in diabetic patients were lower than non-diabetic patients since this difference were not significant. These results are incongruent with the findings of previous studies suggesting a positive correlation between serum phosphate and sclerostin levels in hemodialysis patients (14,18,26). Pelletier et al found a significant positive correlation between serum phosphate and sclerostin levels in patients with chronic renal failure through the multiple regression analysis (14). Desjardins et al showed a positive association between sclerostin level and serum phosphate levels in patients with chronic renal failure (26).Another study supported the positive and significant association among serum phosphate and sclerostin level among the hemodialysis patients (18).These results do not match the result of our study. This discrepancy could be attributed to the use of effective treatments on phosphate and calcium levels in our study. The results of our study showed a negative correlation between serum sclerostin levels and plasma hemoglobin level in non-diabetic and diabetic patients. In contrast, Viaene et al found that high level of hemoglobin is associated with high level of sclerostin in patients (15).

Some studies supported the positive relationship between levels of glycosylated hemoglobin and sclerostin in diabetic patients (27). Further studies however should be conducted to investigate the relationship between sclerostin and anemia and other anemia related factors, such as the number of red blood cells and platelets.

The recent evidence revealed a significant positive association between the dialysis adequacy in diabetic and non-diabetic patients and serum sclerostin levels, which was not in line with those of previous studies (28-30). Some studies indicated a negative association between low- sclerostin levels and dialysis adequacy during hemodialysis. The current study found no significant negative correlation between serum sclerostin level and BMI in all patients. There was a positive correlation between high sclerostin level and BMI, high fat mass, as well as high serum LDL cholesterol (LDL-c) in general population (13). A significant positive correlation was also found between sclerostin level and BMI in postmenopausal women and old men (31, 32), however a previous study showed no relationship was observed between BMI and serum sclerostin level in hemodialysis patients (17). We found no negative correlation between serum sclerostin level and PTH in diabetic patients and in non-diabetics. In a cohort study, Gennari et al measured the sclerostin levels in 40 patients with type 2 diabetes, 43 patients with type 1 diabetes and 83 subjects as the control group. Their results showed a significant negative correlation between sclerostin levels and PTH in healthy non-diabetic patients. Moreover, no significant negative correlation was found in the people with type 2 diabetes, which was not in agreement with the findings of our study (33). Several systemic and local factors have been suggested as possible regulators of SOST/sclerostin expression by osteocytes including PTH. In both in vivo and in vitro, PTH decreases sclerostin expression and secretion (34). PTH suppresses the transcription of SOST gene in vitro (35). Moreover, overexpressed PTH-related protein (PTHrP) markedly decreased the expression and secretion of sclerostin level in mice (34,35). Furthermore, intermittent administration of PTH to rats increased the expression of SOST gene and production and secretion of sclerostin (36). The results of a cohort study on women with osteoporosis and healthy women showed that sclerostin levels are inversely related to PTH levels (29). Patients with primary hyperparathyroidism have lower circulating sclerostin then normal PTH controls (37).

In addition, either intermittent or continuous infusions of PTH (1,34) decreased circulating sclerostin levels in postmenopausal women and healthy men (35). In our

study, serum parathyroid and sclerostin hormones was slightly higher in non-diabetic patients than diabetics, however their difference were not significant. Gennari et al reported that serum sclerostin levels in healthy controls had a significant negative correlation with PTH; however, the relationship was negative and non-significant in diabetic patients. Their result also suggested that subjects with type 2 diabetes, but not those with type 1 diabetes showed higher sclerostin serum levels when compared to healthy matched controls. This means that PTH levels in diabetic patients are higher than those in healthy subjects while PTH inhibited the suppression of sclerostin production (30). The results of our study demonstrated that PTH levels in patients with chronic renal failure were increased compared to patients with chronic renal failure, which may be attributed to the suppression of sclerostin production by PTH in these patients. However, more clinical studies need to be undertaken to support this finding. It was also shown that high doses of sevelamer increased the PTH level in the studied patients; however, sevelamer intake three times per day lowered PTH level. The previous investigations showed, high PTH levels led to the elevation of sclerostin levels. In a cohort study, Kim et al found a significant positive correlation between sclerostin and PTH levels in patients with CKD stages 3 to 5; however, this correlation was not reported in multiple regression analysis. They also demonstrated that kidney failure is likely to lead to the rapid development of bone marrow resistance to PTH and low-parathyroid hormone signaling, resulting in increased sclerostin production in patients with chronic renal failure. They suggested that elevated levels of PTH often are associated with reduced glomerular filtration rate (GFR) (36).

Conclusion

These results outline some conflicting results on the association of sclerostin with nutritional factors and biochemical factors. This rather contradictory result may be due to the use of different populations and the impact of demographic factors, disease stage, type of medications and other factors. The most obvious finding from this study is a positive association between sclerostin and the stage of CKD and the rate of glomerular filtration as well as bone mineral metabolism disorder in patients. It is recommended that further research needs to be undertaken to investigate the effectiveness of sclerostin antagonists in lowering the bone disorders resulting from high sclerostin levels.

Limitations of the study

This is a single-center study, requires further investigation by larger studies.

Authors' contribution

Conceptualization, Methodology, Validation, Resources, Visualization: LM. Formal Analysis, Investigation, Data Curation, Project Administration: HM and LM. Writing—Original Draft Preparation: MM, HM and LM. Writing—Review and Editing, Supervision: MM.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical issues

Human rights were respected in accordance with the Helsinki Declaration 1975, as revised in 1983. The ethical committee of Shahrekord university of medical sciences approved this study (ethical code; IR.SKUMS.REC.1396.152). Informed consent was taken from the patients. Besides, this study was extracted from the M.D., thesis of Hossein Moeini at this university (Thesis#2568). Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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