Zagazig University Medical Journal
www.zumj.journals.ekb.eg

Manuscript ID ZUMJ-1909-1477 (R5)
DOI 10.21608/zumj.2020.16472.1477

ORIGINAL ARTICLE

The Effect of Renal Dysfunction on Circulating Sclerostin Level in Patients with Type 2 Diabetes

Mahmoud Hamdy El-Sebaie[1*], Mohamed Abbas Arafat[2], Mohamed Samy Fawzy[3], Ibrahim Mohamed Salem[2]

1: Resident of internal Medicine, , Ahmed Maher Teaching Hospital, Egypt.
2 : Internal Medicine Department, Faculty of Medicine, Zagazig University, Sharkia Egypt.
3 : Biochemistry Department, Faculty of Medicine, Zagazig University, Sharkia Egypt.

***Corresponding Author:**
Mahmoud Hamdy El-Sebaie
dr_ahmed_hassanin2009@yahoo.com

Submit Date 15-09-2019
Revise Date 31-12-2019
Accept Date 2020-01-07

ABSTRACT

Background: Sclerostin, a soluble canonical Wingless integration site signaling inhibitor, is formed by osteocytes and is vital for bone physiology. This work aimed to appraise the role of sclerostin level in early detection of renal osteodystrophy in patients with type 2 diabetes mellitus (T2DM). **Method:** This cross sectional study was done on 75 diabetic patients with different stages of chronic kidney disease (CKD) in the Internal Medicine department, Zagazig University hospital.The patients are classified into 3 groups according to glomerular filtration rate(GFR),group 1(stage 1,2 CKD),group 2(stage 3 CKD),group 3(stage 4,5 CKD). The patients underwent history taking, examination and laboratory studies including routine investigations and assessment of serum sclerostin. **Results:** The mean age of the patients was 51.07 ± 4.40 years. Males represented 61.3% of them. Mean Sclerostin of them was 5.42 ± 4.53 ng/ml. There are significant differences between groups with different CKD stages regarding sclerostin, hemoglobin, serum creatinine, blood urea, eGFR, phosphorus and parathyroid hormone. There is significant positive correlation between serum sclerostin and all of serum creatinine, blood urea, phosphorus and parathyroid hormone. There is significant negative correlation between it and eGFR. On multivariate regression analysis, it was found that age, serum creatinine, blood urea, eGFR and albumin/creatinine ratio (ACR) significantly associated with serum level. **Conclusion:** Sclerostin level is negatively correlated with eGFR in diabetic patients with impaired renal function. Serum sclerostin levels increase in diabetic patients starting from CKD-G3 stage. Age, serum creatinine, blood urea, eGFR and albumin/creatinine ratio (ACR) significantly associated with its level.

Keywords: Chronic kidney disease; Diabetes; sclerostin

INTRODUCTION

Diabetes mellitus is a group of metabolic ailments characterized by hyperglycemia originating from imperfection in insulin secretion, action or both. The chronic diabetic hyperglycemia is connected with long dated impairment, dysfunction and failure of other organs particularly the eyes, kidneys, nerves and blood vessels[1].

CKD is defined as impairments of kidney function or construction existing for more than 3 months, with health consequences.

This definition covers patients with a glomerular filtration rate (GFR) of < 60 ml/min/1.73 m^2 on at least 2 instances parted by a period of at least 90 days (with or without kidney damage marker). The risk of developing CKD surges with age. With advancement in kidney dysfunction, some simultaneous conditions get commoner and rise in severity. Finally, it can evolute to end-stage kidney disease[(2).]

The prevalence of end-stage renal disease (ESRD) tend to rise, although the incidence has stabilized [(3)].

Metabolic bone disorders in CKD are the consequences of changed mineral and bone metabolism (MBD) due to compromised renal function [(4)].

Bone biopsy is still the gold standard test aimed at categorizing renal osteodystrophy (RO) though more rarely done. The bone turnover rate measured by cycline double labeling and the osteoid thickness are the chief parameters that outline RO forms[(5)].

Sclerostin and Dickkopf-1 (Dkk-1), Wingless integration site (Wnt) inhibitors that decrease bone formation, may play a role in CKD related bone disorders. It can clarify the low bone creation detected in some uremic forms[6]

Basal serum sclerostin level, a marker of bone resorption, is a worthy predictor of bone loss in CKD patients as evaluateded by DEXA or QCT[5]. Overall, those biomarkers can mirror the bone disease severity[7]

This work aimed to appraise the role of sclerostin level in early detection of renal osteodystrophy "bone mineral disease" in patients with type 2 diabetes

Patient and Methods

The work has been carried in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsiniki) for studies involving humans. A written informed consent was handled from the patient to contribute in the study. Approval for execution the research was gotten from Internal Medicine and Medical Biochemistry Departments, Zagazig University Hospitals after receiving Institutional Review Board (IRB) approval.

Study Design, Study Setting, and Study Participants

A cross-sectional study was conducted in Internal Medicine department at Zagazig University through the period of September 2018 to February 2019. This study included 75 T2DM patients with CKD who visited the endocrinology or nephrology clinic.

Sample size:

Assuming that mean±SD of serum sclerostin level in G1,2 CKD versus G3 CKD is 54.6±6.9 vs 60±9.2, the sample was calculated to be 75 patients using OPEN-EPI with power 80% and confidence interval 95%. The patients were selected by systematic random technique

Inclusion criteria

Ages from 35 to 65 year
Normal liver function
Duration of diabetes more than 5 years

Exclusion criteria

Other chronic diseases
Well-known syndromes affecting bone
Previous or current treatment with drugs distressing bone metabolism.

Study Assessments and Data Collection

For each eligible patient, we reported the following data:

History

Detailed history taking include name, age, sex, special habits, associated comorbidities, diabetes mellitus index (duration, type, medication).

Full general examination and ***Staging of CKD***

CKD is classified into 5 stages. This classification uses the combination of an index of kidney function, GFR, and markers of kidney damage to define the stages. Stages 3–5(stage 3:GFR 30 to 59,stage 4:GFR 15 to 29,stage 5:GFR less than 15) were defined by a GFR less than 60 ml/min/1.73 m2 with or without markers of kidney damage, on at least 2 separate occasions separated by a period of at least 90 days. Stages 1 and 2(stage 1:GFR more than 90 ml/min/1.73 m2,stage 2:GFR 60 to 89 ml/min/1.73 m2) were defined by the presence

of markers of kidney damage including albuminuria, urine sediment abnormalities, electrolyte and other abnormalities caused by tubular disorders, abnormalities detected by histology and structural abnormalities detected by imaging [8].

Laboratory investigations:

Venous blood samples were withdrawn in the morning following overnight fasting. Sera were stored at −80∘C until examination. The routine laboratory investigations were done according to Clinical Pathology department and laboratories of Zagazig University Hospitals' protocol and include:

Complete blood count (CBC): measured by automated blood counter (by sysmex XN 2000).

Kidney function tests: serum creatinine, serum urea and uric acid by colorimetric assay (by cobas 8000 series module C 702).

Liver function tests: serum albumin, total protein, bilirubin, AST and ALT by colorimetric assay (by cobas 8000 series module C 702).

Calcium and phosphorous (by cobas 8000 series module C 702).

PTH (by cobas 6000 series module e 601)

Estimated glomerular filtration rate (eGFR) using MDRD equation: eGFR = 175 x $(Cr)^{-1.154}$ x $(Age)^{-0.203}$ x (0.742 if female) x (1.210 if black)

Albumin creatinine ratio (ACR) (by cobas 6000 module C 501).

Random blood Sugar (by cobas 8000 series module C 702).

HbA1c (by cobas 6000 module C 501).

CRP (by cobas 8000 series module C 702).

Serum sclerostin level was assessed using enzyme-linked immune sorbent assay (ELISA). The assay was carried out by Human Sclerostin (SOST) ELISA Kit by AndyGene Biotechnology Co., LTD, Shanghai

Statistical Analysis

All data were gathereed, tabulated and statistically analyzed using SPSS 20.0 for windows (SPSS Inc., Chicago, IL, USA) & MedCalc 13 for windows (MedCalc Software bvba, Ostend, Belgium). Data were tested for normal distribution using the Shapiro Walk test. Qualitative data were symbolized as frequencies and relative percentages. Chi square test ($\chi 2$) was used to compute difference between qualitative variables. Quantitative data were stated as mean ± SD (Standard deviation). Mann Whitney test was used to compare medians of two groups (for nonparametric data).One way ANOVA test was used to compare between more than two dependent groups of normally distributed variables while Kruskal Wallis test ranks test was used for non-normally distributed variables. Pearson's and Spearman correlation tests were used for correlating normal and non-parametric variables respectively. Multivariate regression analysis (stepwise method) was performed to ascertain factors associated with sclerostin levels. All statistical comparisons were two tailed with significance Level of P-value ≤ 0.05 is significant and p ≤0.001 is highly significant difference.

RESULTS

The present study comprised 75 patients with diabetes. Their mean age of 51.07 ± 4.40 years. The largest percentage of the studied patients were male (61.3%), about 47% of them had comorbid hypertension and 18.7% of them had history of ischemic heart disease. The baseline characteristics were reported in (**Table 1**).

Mean Sclerostin of the studied patients was 5.42 ± 4.53 ng/ml ranging from 0.097 – 22.04 ng/ml. There is a statistically significant relation between the studied groups with different stages of CKD and sclerostin level. Highest level was among patients with stage 5. However, there is non-significant relation between gender and serum sclerostin level (**Table 2).**

There is statistically significant difference between patients with different CKD stages regarding hemoglobin level which was lower in patients with grade 5 as found in post hoc test (Table 3)

There is statistically significant difference between patients with different CKD stages

regarding serum creatinine, blood urea levels, eGFR, Po4 and parathyroid hormone level. On doing posthoc test, the difference is significant patients with stage 5 and each other group regarding serum creatinine and eGFR while the difference is significant between each two groups regarding PTH and phosphorus. The group of stage 1 CKD ahd the lowest blood urea level (Table 3**)**

On the other hand, there is no difference between patients with stages of CKD regarding demographic characteristics, TLC, platelet count, liver function test, random blood sugar, HbA1c, ACR, serum calcium or CRP (Table 3)

There is significant positive correlation between serum sclerostin and all of serum creatinine, blood urea, Po4 and serum parathyroid hormone. There is also significant yet negative correlation between it and eGFR. On the other hand, there is non-significant correlation between serum sclerostin and other studied parameters (**Table 4)**.

On multivariate regression analysis of factors independently associated with serum sclerostin, it was found that age, serum creatinine, blood urea, eGFR and ACR found to be significantly associated with serum level (Table 5).

Table 1. Demographic data and comorbidities of all patients

		All patients (n=75)
Age*(years)* *Mean ± SD* *Range*		51.07 ± 4.40 43 - 59
Sex	*Male*	46 (61.3%)
	Female	29 (38.7%)
HTN		35 (46.7%) (Male:20) (Female:15)
IHD		14 (18.7%) (Male:8) (Female:6)

IHD ischemic heart disease HTN hypertension

Table 2. Serum sclerostin of all patients and distribution according to grades of Nephropathy

P	***test***	***Stage 5 (n=8)***	***Stage 4 (n=20)***	***Stage 3 (n=22)***	***Stage 2 (n=18)***	***Stage 1 (n=7)***	***Variable***
0.001	**37.61**	15.18±3.17	7.18 ± 1.55	3.86 ±0.75	1.52±0.66	0.14 ± 0.06	*Sclerostin*

p	***Total***	***Females*** *(n=29)*	***Males*** *(n=46)*	***Variable***
0.638	5.42 ± 4.53	5.07 ± 4.12	5.62 ± 3.65	***Sclerostin(ng/mL)***

Table 3. Comparison between patients according to GFR stages regarding demographic and laboratory characetristics

Variable		*Stage 1 (n=7)*	*Stage 2 (n=18)*	*Stage 3 (n=22)*	*Stage 4 (n=20)*	*Stage 5 (n=8)*	*Test*	*P*
		Mean± SD	***Mean± SD***	***Mean± SD***	***Mean± SD***	***Mean± SD***		
Demographic criteria								
***Age** (years)*		46.6 ± 5.13	52.2 ± 4.17	50.6 ± 4.47	50.5± 4.72	52.0± 4.39	0.75	0.53
Sex	*Male*	5(71.4%)	8 (44.4%)	15 (68.2%)	11(55%)	7(87.5%)	4.175	0.084
	Female	2(28.6%)	10 (55.6%)	7 (31.8%)	9(45%)	1(12.5%)		
BMI		28.1 ± 2.24	26.5 ± 1.79	27.2 ± 1.51	26.4 ± 1.71	25.4 ± 2.53	2.015	0.12
CBC								
Hemoglobin		11.9 ±0.65	12.25 ±0.59	11.5 ± .89	11.49 ± .87	9.45±0.59	**3.96**	**0.012**
TLC		7.14 ± 2.07	7.13 ± 1.25	6.96 ± 1.56	7.12 ± 1.63	7.02±1.72	0.065	0.98
Platelet count		269.4±85.1	284.8±79.9	274.7±74.2	277.1±78.8	273.2±77.09	0.087	0.97
Liver functions								
T. Bilirubin		0.90 ± 0.28	0.86 ±0.16	0.87 ± 0.19	0.86 ± 0.21	0.91±0.17	0.061	0.98
D. bilirubin		0.16 ± 0.04	0.16 ±0.07	0.15 ± 0.05	0.14 ±0.06	0.16±0.07	0.27	0.85
Albumin		4.38 ±0.59	4.32 ±0.55	4.33 ± 0.55	4.21 ± 0.49	4.07±0.75	0.035	0.99
Total protein		6.94 ±0.34	7.02 ±0.53	7.0 ± 0.49	6.97 ± 0.51	6.85±0.30	0.046	0.98
AST		20.6 ± 8.53	17.9 ± 5.74	18.4 ± 6.28	17.67 ± 5.7	19.23±4.65	0.34	0.79
ALT		32.0 ± 7.94	27.75 ± 7.09	28.6 ± 7.29	28.05 ± 6.99	31.13±8.46	0.49	0.69
Diabetic follow up								
RBS		225.8±15.7	226.6±18.8	226.4±17.9	224.5±17.9	243.3±10.32	0.059	0.91
HbA1c		7.02 ± 0.29	6.88 ± 0.28	6.91 ± 0.28	6.89 ±0.27	6.81±0.26	0.35	0.79
Kidney function								
ACR		173.6±9	152.9±13	202.5±9	167.9±	119.4±11	0.71	0.55

	8.4	2.9	7.3	127.6	0.2		
Creatinine	0.86 ± .114	0.975 ± .141	1.76 ±0.19	2.93 ±0 .21	4.60±0.63	**46.19**	**<0.001**
Urea	37.2 ± 6.34	32.2 ± 6.73	62.7 ± 7.08	98.8 ± 7.14	99.10±6.9 4	**38.36**	**<0.001**
eGFR	98.5 ± 6.78	77.1 ± 7.24	40.2 ± 5.35	21.6 ± 3.29	12.69±1.2 2	**49.21**	**<0.001**
Mineral and parathyroid profile							
Phosphorus	3.38 ± 0.46	3.87 ± 0.67	4.02 ± 0.72	4.63 ± 0.85	5.69±1.23	**12.07**	**<0.001**
Parathromo ne	34.4 ± 15.3	63.4 ± 27.6	84.8 ± 30.2	169.8 ± 69.9	413.6±30 6.1	**19.85**	**<0.001**
Calcium	9.10 ±0 .42	8.96 ± 0.43	8.96 ± 0.40	8.82 ± 0.59	8.39±0.69	0.82	0.13
CRP	5.80 ± 1.64	6.75 ± 1.65	6.56 ± 1.66	6.52 ± 1.75	6.7±1.38	0.43	0.73

TLC total leucocytic count eGFR estimated glomerular filtration rate, ACR: albumin creatinine ratio, PTH: parathyroid hormone $p<0.05$ is statistically significant HbA1c: glycosylated hemoglobin BMI: body mass index

Table 4. Correlation of Sclerostin with other parameters

		Sclerostin
Age	*r*	0.120
	p	0.317
BMI	*r*	-0.138
	p	0.249
Hemoglobin	*r*	0.077
	p	0.526
TLC	*r*	0.002
	p	0.985
Platelet	*r*	0.041
	p	0.733
ACR	*r*	-0.126
	p	0.294
T. Bilirubin	*r*	0.083
	p	0.491
D. Bilirubin	*r*	0.129

	p	0.284
Albumin	*r*	-0.077
	p	0.523
Total protein	*r*	-0.081
	p	0.502
AST	*r*	0.131
	p	0.276
ALT	*r*	-0.205
	p	0.087
Random blood sugar	*r*	0.114
	p	0.344
HbA1C	*r*	0.002
	p	0.986
CRP	*r*	0.093
	p	0.440
Calcium	*r*	-0.254
	p	0.196
Creatinine	*r*	**0.895**
	p	**< 0.001**
Urea	*r*	**0.759**
	p	**< 0.001**
eGFR	*r*	**-0.786**
	p	**< 0.001**
Phosphorus	*r*	**0.584**
	p	**< 0.001**
Parathromone	*r*	**0.662**
	p	**< 0.001**

r correlation coefficient SE standard error of mean eGFR estimated glomerular filtration rate, ACR: albumin creatinine ratio, PTH: parathyroid hormone $p<0.05$ is statistically significant HbA1c: glycosylated hemoglobin BMI: body mass index

Table 5. Multivariate regression analysis to identify factors influencing sclerostin levels

	Unstandardized Coefficients		*Standardized Coefficients*	*p*	*95.0% Confidence Interval for β*	
	β	**S.E**	**β**		**Lower Bound**	**Upper Bound**
Hemoglobin	-.554	.363	-.136	.133	-1.283	.175
Phosphorus	-.213	.484	-.041	.661	-1.183	.757
PTH	-.055	.029	-.212	.061	-.112	.003
Age	-.082	.064	-.107	**.027**	-.212	.047
Creatinine	3.787	1.449	.900	**.012**	.882	6.692
Urea	.004	.039	.035	**.029**	-.083	.074
eGFR	-.014	.024	-.105	**.007**	-.034	.062
ACR	.004	.002	.121	**.044**	-.001	.008

SE standard error of mean eGFR estimated glomerular filtration rate, ACR: albumin creatinine ratio, PTH: parathyroid hormone $p<0.05$ is statistically significant

Age, creatinine, urea, eGFR and ACR found to be significantly associated with sclerostin levels.

DISCUSSION

Sclerostin, a glycoprotein which is produced almost only by osteocytes. It negatively regulates bone production by tying to low-density lipoprotein receptor-related proteins (LRPs) 5/6 and by antagonizing the Wnt-catenin signaling pathway. Wnt/β-catenin signaling pathway is a molecular trail recognized to be critical bone mineral physiology regulation. Wnt ligands fix to LRP 5/6 membrane receptor complex ending in increasing bone formation[9].

The effect of wnt signaling on bone is facilitated by probing stem cell and preosteoblast multiplicationg, induction of osteoblastogenesis, and stopping osteoblast and osteocyte apoptosis [10].

In healthy subjects, circulating sclerostin concentration has been described to be greater in males. Sclerostin level positively correlates with age, BMI, and BMD. Serum sclerostin level increase with advanced age and in subjects with high BMI and high BMD[11].

To the best of our knowledge, there are few studies in the literarture that revealed the association of serum sclerstin levels in with different liver and kidney fuctions tests in CKD patients. Serum sclerostin level increase with deterioration of liver and kidney functions.

In our study, as regarding the demographic data, the mean age of the studied subjects was 51.07 ± 4.40 years and among them there were 46 males and 29 females.

This came opposite to **Kim et al.** [(12)] who evaluated serum sclerostin level reagrding renal function in T2DM patients and the mean age within their study was higher (67.4 ± 7.3 years). Male and female distribution (143 males and 159 females) that was inverse to our results.

There is no statistical significant difference between studied groups\with different CKD stages regarding the age or random blood sugar.

In the current study, the mean value of sclerostin was 5.42 ± 4.53 ng/ml. **Kim et al.** [(12)] found that median sclerostin level in their patients was 28.66 ng/ml.

There was a highly significant difference in sclerotin serum levels between the different CKD subgroups, being higher in G5 group.

This agreed with the results of **Cejka et al.** [(13)] who found that patients CKD, stage 5 on dialysis had higher sclerostin levels and

submitted that raised up sclerostin has a role in ROD. They stated that sclerostinhad a significant negative association with bone turnover parameters.

This also came in consistent with another study who showed that sclerostin was significantly rising in patients with G4/5 or G3 after adjusting for age, sex, and BMI (225.5 ± 10.9 versus 84.9 ± 9.2 versus 54.6 ± 6.9 pmol/l)[12].

Our study showed that there is a significant difference between the GFR groups regarding hemoglobin, creatinine, urea, eGFR, phosphorus, PTH and sclerostin.

Sabbagh et al. [14] conveyed that osteocytes suppression Wnt-catenin signaling and higher expression of sclerostin happened in early stage of CKD in a genetic model of mice. They advocated that subjugation of the Wnt-catenin pathway is an early incident in the evolution of ROD.

Cejka et al. [13] found that higher sclerostin in CKD patients were not owing to diminished renal excretion. However, augmented circulating sclerostin is due increased sclerostin formation in uremic patients.

Our study showed that there is a significant positive correlation between sclerostin with creatinine, urea, ACR, phosphorus and PTH and a negative correlation with age, BMI, hemoglobin, eGFR and calcium.

In this study, there was a positive correlation between age and serum sclerostin levelsin agreement with other studies [15-16].

Serum sclerostin level upsurges considerably with age in healthy pre and postmenopausal females. Serum sclerostin rises over life by about 3.7-fold. Raising sclerostin formation by osteocytes may be tangled in the age-related deficiency of bone formation [17].

Elderly patients have strikingly diminished renal function. The positive relationship between sclerostin and age could be originating from renal impairment, which is not precisely evaluated in other diseases. Osteoporosis in elderly may partially result from rising sclerostin owing to an undervalued renal impairment.

We found a highly significant negative correlation between the serum sclerostin levels and eGFR.

This came in accordance with **Cejka et al. [13]** who revealed that renal sclerostin excretion up rises with diminishing renal function. Both relative and absolute sclerostin levels eliminated by the kidneys rise with declining eGFR.

We reported that increased serum levels are thanks to higher sclerostin formation in uremic patients, as has been submitted by **Sabbagh et al. [15]**.

The current study came in consistent with **Pelletier et al. [14]** who found that serum sclerostin levels rises as eGFR reduced in CKD patients. Still, it was unidentified whether this result relates to the patients with T2DM.

The core mechanisms of higher levels of sclerostin in ckD are unknown. PTH receptor signaling is a recognized sclerostin expression inhibitor. As uremia causes PTH opposition, reducing PTH signaling activity might end in increased fabrication of sclerostin in CKD patients [14].

In the current study, a highly significant positive correlation between the serum sclerostin levels and PTH levels was detected. This came in harmony with **Kim et al. [12]** who reported a positive correlation between sclerostin and PTH in patients with CKD-G3-5.

Our results disagreed with the results of many studies that have shown inverse correlation between serum sclerostin and PTH level [13,15,18].

Contradictory results were also reported by **Thambiah et al. [19]** have shown reverse correlation between serum sclerostin and PTH level. ***Mirza et al. [20]*** stated that sclerostin levels inversely correlated with PTH in postmenopausal women short of CKD.

The discrepancy of the results could be attributed to that renal failure ends in skeletal resistance to PTH, and reducings in PTH signaling activity might result in increased production of sclerostin in CKD patients. The actions of PTH on bone are mediated, at least

partly, through decreasing of sclerostin expression [(18)].

There was a positive correlation between the serum sclerostin levels and serum phosphorous levels in our patients.

Additional study reported that serum phosphate was independently associated with sclerostin [(15)].

Similarly, this came in accordance with **Ferreira et al. [(21)]** as they reported that dietary phosphate motivated bone sclerostin expression irrespective of PTH in a model of CKD-adynamic bone disease.

We partially settled with **Kim et al. [(12)]** where there was a weak correlation between serum phosphate and sclerostin.

This proposes that increases in phosphorus and sclerostin levels in CKD patients happened simultaneously but are not essentially mechanistically related [(6)].

Hwever, **Cejka et al. [(13)]** stated that there was no relation between serum sclerostin and fractional excretion of phosphate.

By the multivariate analysis, the correlation between serum phosphorous and serum sclerostin could be explanied due to effect of age and reduction of eGFR and it wasn't an independent risk factor.

This part are not in consistent with former study in which a positive relation between serum phosphate and sclerostin, regardless GFR, may have clinical importance[(18)].

Indeed, **Hruska and Mathew [(22)],** by adjusting serum phosphate via phosphate binders, inverted CKD-ledd trabecular osteopenia and so augmented osteoblast surfaces in the metaphyseal trabeculae of tibia and femur, osteoid surfaces, and bone formation rates.

Garcia-Martin et al. [(23)] found that serum sclerostin significantly correlated with diabetes duration and glycated hemoglobin in T2DM patients in disagreement with our study.

Our study showed that there is a positive correlation between sclerostin with creatinine. This came in consistent with a cohort conducted by **Kim et al. [(12)]**

We found that age, urea and ACR were found to be significantly associated with sclerostin levels. No significant correlation was revealed in our study as regarding the effect of gender on the serum levels of sclerostin.

Modder et al. [(16)] disagreed with our results as men had higher circulating sclerostin levels in a population sample. **Kirmani et al. [(24)]** demonstrated that serum sclerostin levels were higher in boys aged 6–21 years.

In our study, no significant inverse correlation was found between BMI and serum sclerostin levels.

Serum sclerostin negatively correlated with PTH but not with alkaline phosphatases or DKK-1 [25-26].

This came in opposite to the results by **Kim et al. [(12)]** found that BMI showed negative correlation with serum sclerostin in all patients, but it positively correlated with sclerostin in patients with G1/2..

CONCLUSION

By the end, we concluded that sclerostin level is negatively correlated with eGFR in diabetic patients with impaired renal function. Serum sclerostin levels increase in diabetic patients starting from CKD-G3 stage. Age, serum creatinine, blood urea, eGFR and albumin/creatinine ratio (ACR) significantly associated with its level.

This study had some limitations; including being cross sectional study, relatively small sample size and lack of control group. Further large scale prospective studies should be applied to establish role of serum sclerostin level.

Conflict of interest: Nothing to declare

Financial disclosure: Nothing to declare

REFERENCES

1. **American Diabetes Association Standards of Medical Care in Diabetes**. Promoting Health and Reducing Disparities in Populations. *Diabetes Care*. 2017; 40 (Suppl. 1): S6-S10
2. **Al-Barshomy SM, Kamal NM, Elsayed M, Amr GE.** Study of plasma osteoprotegerin and arterial stiffness in chronic kidney disease and hemodialysis patients. IJAR. (2016); 4 (5): 739-746.

3. **United States Renal Data System.** USRDS Annual Data Report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. 2017; 212: 218.
4. **Cozzolino M, Ureña-Torres P, Vervloet MG, Brandenburg V, Bover J, Goldsmith D, et al.** Is chronic kidney disease-mineral bone disorder (CKD-MBD) really a syndrome?". Nephrology Dialysis Transplantation. 2014; 29(10): 1815-1820.
5. **Malluche HH, Davenport DL, Cantor T, Monier-Faugere MC.** Bone mineral density and serum biochemical predictors of bone loss in patients with CKD on dialysis. *Clin J Am Soc Nephrol*. 2014; 9(7): 1254–1262.
6. **Vervloet MG, Massy ZA, Brandenburg VM, Mazzaferro S, Cozzolino M, Ureña-Torres P, et al.** Bone: a new endocrine organ at the heart of chronic kidney disease and mineral and bone disorders." The lancet Diabetes & endocrinology. 2014; 2(5): 427-436.
7. **Cohen-Solal M and Torres PAU.** Vitamin D and Bone in Chronic Kidney Disease Vitamin D in Chronic Kidney Disease. Springer. 2016; 217-228
8. **Uhlig K, Berns JS, Carville S, Chan W, Cheung M, Guyatt GH, et al.** Recommendations for kidney disease guideline updating: a report by the KDIGO Methods Committee. Kidney Int. 2016; 89(4):753-760.
9. **Baron R and Rawadi G.** Minireview: targeting the Wnt/_-catenin pathway to regulate bone formation in the adult skeleton. Endocrinology. 2007; 148(6): 2635-2643
10. **Krishnan V, Bryant HU, Macdougald OA.** Regulation of bone mass by Wnt signaling. J Clin Invest. 2006; 116(5):1202–1209.
11. **Amrein K, Amrein S, Drexler C**, **Dimai HP, Dobnig H, Pfeifer K, et al.** Sclerostin and its association with physical activity, age, gender, body composition, and bone mineral content in healthy adults J Clin Endocrinol Metab. 2012; 97(1): 148-154.
12. **Kim CA, Honjo R, Bertola D, Albano L, Oliveira L, Jales S, et al.** A known SOST gene mutation causes sclerosteosis in a familial and an isolated case from Brazilian origin." Genet Test. 2008; 12(4): 475-479.
13. **Cejka D, Herberth J, Branscum AJ, Fardo DW, Monier-Faugere MC, Diarra D, et al.** Sclerostin and Dickkopf-1 in renal osteodystrophy." Clin J Am Soc Nephrol. 2011; 6(4): 877-882.
14. **Sabbagh Y, Graciolli FG, O'Brien S, Tang W, dos Reis LM, Ryan S, et al.** Repression of osteocyte Wnt-catenin signaling is an early event in the progression of renal osteodystrophy. J Bone Miner Res. 2012; 27(8): 1757-1772.
15. **Pelletier S, Dubourg L, Carlier MC, Hadj-Aissa A, Fouque D.** The relation between renal function and serum sclerostin in adult patients with CKD. *Clin J Am Soc Nephrol*. 2013; 8(5): 819–823.
16. **Modder UI, Hoey KA, Amin S, McCready LK, Achenbach SJ, Riggs BL, et al.**Relation of age, gender, and bone mass to circulating sclerostin levels in women and men. Journal of Bone and Mineral Research. 2011; 26(2): 373-379.
17. **Ardawi HA, Al-Kadi, Rouzi AA, and Qari MH.** "Determinants of serum sclerostin in healthy pre- and postmenopausal women," J Bone Miner Res. 2011; 26(12): 2812–2822.
18. **van Lierop, Witteveen JE, Hamdy NAT, and Papapoulos SE.** "Patients with primary hyperparathyroidism have lower circulating sclerostin levels than euparathyroid controls," European Journal of Endocrinology. 2010; 163(5): 833–837.
19. **Thambiah S, Roplekar R, Manghat P, Fogelman I, Fraser WD, Goldsmith D et al..** Circulating sclerostin and Dickkopf-1 (DKK1) in predialysis chronic kidney disease (CKD): relationship with bone density and arterial stiffness. Calcif Tissue Int. 2012; 90: 473–480**.**
20. **Mirza, Padhi ID, Raisz LG, and Lorenzo JA.** "Serum sclerostin levels negatively correlate with parathyroid hormone levels and free estrogen index in postmenopausal women," . J Clin Endocrinol Metab. 2010; 95(4): 1991–1997.
21. **Ferreira, Ferrari GO, and Neves KR.** "Effects of dietary phosphate on adynamic bone disease in rats with chronic kidney disease—role of sclerostin?" PLoS ONE. 2013; 8(11): e79721.
22. **Hruska KA, Mathew S**. The roles of the skeleton and phosphorus in the CKD mineral bone disorder. *Adv Chronic Kidney Dis.* 2011; 18(2): 98104.
23. **Garcia-Martin A, Rozas-Moreno P and Reyes-Garcia R.** Circulating levels of sclerostin are increased in patients with type 2 diabetes

mellitus. J Clin Endocrinol Metab. 2012; 97(1): 234-241.

24. **Amin SK, McCready LK, Atkinson EJ, Melton III LJ, Müller R, et al.** "Sclerostin levels during growth in children," Osteoporosis International. 2012; 23(3): 1123–1130.
25. **Viaene L, Behets GJ, Claes K, Meijers B, Blocki F, Brandenburg V, et al.** Sclerostin: another bone-related protein related to all-cause mortality in haemodialysis?". Nephrology Dialysis Transplantation. 2013; 28(12): 3024-3030.
26. **Drechsler C, Evenepoel P, Vervloe MG, Wanner C, Ketteler M, Marx N, et al.** High levels of circulating sclerostin are associated with better cardiovascular survival in incident dialysis patients: results from the NECOSAD study." Nephrology Dialysis Transplantation. 2014; 30(2): 288-293.

Cite This Article

El sebaie, M., arafat, M., fawzy, M., salem, I. The Effect of Renal Dysfunction on Circulating Sclerostin Level in Patients with Type 2 Diabetes. *Zagazig University Medical Journal*, 2021; (58-69): -. doi: 10.21608/zumj.2020.16472.1477