

Plasma Sclerostin Level in Multiple Myeloma: Correlations with Disease Features and International Staging System

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Abstract

Background: Multiple myeloma (MM) is a heterogeneous plasma cell malignancy with various complications. Sclerostin is a Wingless-type (Wnt) inhibitor specifically expressed by osteocytes; it acts as a negative regulator of bone formation. **Objectives:** To assess plasma sclerostin level in MM patients and find its correlations with clinical and laboratory data, including osteolytic bone disease and international staging system (ISS). **Materials and Methods:** This cross-sectional study included 80 individuals: 40 newly diagnosed MM patients and 40 healthy adults. Patients were divided according to the presence of bone disease and ISS stage and were investigated for complete blood count, blood film and bone marrow (BM). Plasma levels of β 2-microglobulin and sclerostin were measured using competitive and sandwich enzyme immunoassay techniques, respectively. **Results:** Sclerostin level was significantly increased in MM patients than control group ($P < 0.001$) and was significantly higher in those with osteolytic bone disease and/or pathological fractures than those without bone lytic lesions ($P < 0.001$). Patients with ISS stage III showed significantly higher sclerostin level than stages I and II ($P = 0.003$). High sclerostin levels were positively correlated with blood urea, serum creatinine, uric acid, and β 2-microglobulin (P -values 0.034, <0.001 , <0.018 and <0.001 , respectively) and negatively with glomerular filtration rate ($P = 0.001$). No significant correlation was found with age, gender, hematological and other biochemical parameters. **Conclusions:** In newly diagnosed MM patients, the plasma sclerostin was significantly correlated with renal impairment. High levels of plasma sclerostin were also found in advanced disease stage and with the presence of significant bone disease.

Keywords: Bone disease, multiple myeloma, sclerostin

INTRODUCTION

Multiple myeloma (MM) is a malignant B-cell neoplasm that is characterized by clonal expansion of plasma cells in the bone marrow (BM) with subsequent production of monoclonal immunoglobulins ultimately causing various complications and organs dysfunction including anemia; renal dysfunction or failure; bone involvement including osteopenia, lytic lesions, pathological fractures; hypercalcemia; immunodeficiency and various infectious complications.^[1,2]

The most common complication of MM is Myeloma bone disease (MBD) which results from uncoupled bone formation and resorption causing osteolytic lesions and pathological fractures that rarely heal even in patients with complete remission contributing to an impaired quality of life increased morbidity, and mortality. Current anti-myeloma

regimens have increased the life expectancy for MM patients but have minor effects on bone repair and patients continue to suffer from the devastating skeletal sequelae. Thus, a key pitfall in controlling MBD is evident.^[3,4]

Osteocytes have emerged as key regulators of bone loss through the secretion of receptor activator of nuclear factor- κ B ligand (RANKL), sclerostin, dickkopf-1 (DKK-1) and other not very well studied factors.^[3,5]

Sclerostin is an osteocyte product encoded by the *SOST* gene and associated with abnormal bone remodeling; it is a

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strong negative regulator of osteoblast differentiation and bone formation, it impedes the activation of the canonical Wnt pathway and inhibits osteoblast maturation, impairs bone mineralization and induces osteoblast apoptosis.^[6,7] The highly specific expression pattern and the exclusive bone phenotype have made Sclerostin an attractive target for therapeutic intervention in treating metabolic bone diseases and fracture repair. Human and animal studies have shown that antibody-mediated inhibition of sclerostin results in significant increase in bone mineral density.^[8,9]

MATERIALS AND METHODS

This cross-sectional study included 40 adult patients with newly diagnosed symptomatic MM, before the administration of any type of therapy. From each participant, detailed history was obtained and physical examination was performed. Hematological and biochemical data monoclonal component and radiological findings were all collected from patients' records. Estimated glomerular filtration rate (GFR) was calculated using the MDRD equation.^[10] Skeletal survey was done to all patients and according to the radiological evidence of osteolytic bone disease; they were divided into two groups: Group A included patients with no osteolytic lesion (no bone involvement $\pm$ osteoporosis only) and group B included patients with osteolytic bone lesions $\pm$ osteoporosis $\pm$ pathological fractures. Patients taking pharmacological estrogen, vitamin D, PTH treatment, or on long-term steroid therapy and patients with other malignancies were excluded from the study. A total of 40 apparently healthy age- and sex-matched individuals were included in this study as a control group.

Complete blood count was done using Hematology ADVIA analyzer (Siemens, Germany). Blood and BM smears were prepared using the standard procedures and the BM plasma cell percentage was determined. Plasma beta-2-microglobulin (β 2M) was assessed by competitive enzyme-linked immunosorbent assay (ELISA) using Human β 2M Quantikine Immunoassay kit (RandD, USA), and plasma sclerostin level was determined by sandwich ELISA using the Human SOST Quantikine Immunoassay kit (RandD, USA).^[11,12]

Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 24.0 for windows. Data was presented as mean $\pm$ SD, median, IQR (interquartile range) and range for quantitative variables and as number and percentage for qualitative variables. Mann Whitney *U*-test was used to test the statistical significance of the nonparametric variables. Spearman correlation test was used to test the correlations between different hematological and biochemical parameters. *P* value of <0.05 was considered statistically significant.

Ethical approval

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. It was carried out with patients verbal and analytical approval before sample was taken. The study protocol and the subject information and consent form were reviewed and approved by a local ethics committee according to the document number 1834 in 5/8/2018.

RESULTS

The mean age for patients was 61.4 ± 14.2 years ranged from 38–90 years. Out of the 40 newly diagnosed myeloma patients, 19 were males (47.5%) and 21 were females (52.5%) with a male to female ratio of 1: 1.1.

Clinically, bone pain was the most common (87.5%) followed by pallor (82.5%) neurological manifestation (25%), fractures (15%) and fever (7.5%). The neurological manifestations were radicular pain in 5 patients, paresis in 4 patients and paraplegia in 1 patient. Anemia was a common finding and 29 patients (72.5%) had their Hb level below 10 g/dL. Neutropenia and thrombocytopenia were not that common with only 4 patients (10%) had an absolute neutrophil count (ANC) $< 2 \times 10^9$ /L and 3 patients (7.5%) had platelet count $< 100 \times 10^9$ /L. Fifteen patients (37.5%) had their serum creatinine > 2 mg/dL, hypercalcemia and hyperuricemia were observed in 11 patients (35%), and 16 patients (40%), respectively. Details of laboratory parameters are shown in [Table 1].

In assessment of renal function, the mean GFR level was 50.5 ± 39.9 mL/min/1.73 m² and ranges from 3–154 mL/min/1.73 m². Renal insufficiency was a common finding in the studied MM patients with 65% had their GFR < 60 mL/min/1.73 m².

Serum Monoclonal immunoglobulin band was detected in all but one of the patients. Immunofixation revealed that

Table 1: Hematological and biochemical parameters in 40 MM patients

Laboratory Findings	Mean $\pm$ SD	Range
Hematological Parameters		
Hb (g/dL)	8.65 ± 1.85	4.84–13
ANC ($\times 10^9$ /L)	4.04 ± 2.04	1.1–11
Platelet ($\times 10^9$ /L)	230 ± 112	44–574
ESR (mm/1 st hour)	111.5 ± 33.5	25–150
BM plasma cell (%)	42.5 ± 21.64	11–90
Biochemical Parameters		
Blood urea (mg/dL)	80.08 ± 67.05	10.4–283.0
Serum creatinine (mg/dL)	2.47 ± 2.74	0.56–13
Serum albumin (g/L)	31.37 ± 9.5	6–47
Serum calcium (mg/dL) ^a	10.2 ± 2.2	7.1–16
Serum uric acid (mg/dL) ^b	6.7 ± 3.7	2.4–21.2
β 2-microglobulin (μ g/mL)	10.4 ± 5.5	2.3–19.3

^a Normal Range (8.4–10.4 mg/dL)

^b Normal Range (2.5–7.2 mg/dL)

out of 40 newly diagnosed MM patients, 33 were of IgG type (82.5%), 6 were IgA (15%) and only one patient had light chain myeloma (2.5%).

Skeletal surveys showed that 87.5% of patients had bone involvement; 29 patients fall in group B who had osteolytic lesions; 6 of them were having pathological fractures (15%) and 3 patients had both lytic lesions and osteoporosis. Group A included 11 patients with no osteolytic lesions; 6 of them had only osteoporosis and in 5 patients no bone involvement was observed [Table 2]. Nine patients had osteoporosis $\pm$ lytic lesions (22.5%).

Thirty of the studied myeloma patients fall in stage III (75%), while 8 patients (20%) were in stage II and only two patients (5%) were in stage I.

In MM patients, the mean of plasma sclerostin level was 883.39 ± 242.22 pg/mL with a range of 387.53–1208.06 pg/mL. The median level (IQR) was 862.26 pg/mL (88.8 pg/mL). While in normal control group, the mean was

336.46 ± 108.47 pg/mL with a range of 239.89–560.32 pg/mL. The median (IQR) level was 368.75 pg/mL (148.9 pg/mL). There was a statistically significant difference in sclerostin levels between patients and control groups with p -value < 0.001 , [Figure 1].

The mean sclerostin level in females was 924.81 ± 183.17 pg/mL and in males it was 867.72 ± 203.8 pg/mL. No statistically significant difference in plasma sclerostin was found according to gender ($P = 0.784$).

Correlation analysis showed that plasma sclerostin levels were positively correlated with serum uric acid ($P = 0.018$), blood urea ($P = 0.034$), serum creatinine ($P < 0.001$) and $\beta 2M$ ($P < 0.001$). Plasma sclerostin levels showed strong negative correlation with GFR ($P = 0.001$). No correlation was found between plasma sclerostin level and other parameters including age, Hb concentration, ANC, platelets count, ESR, BM plasma cell percentage, serum albumin and serum calcium [Table 3].

The mean of plasma sclerostin in group A patients was 665.94 ± 206.77 pg/mL, whereas in group B it was 1020.98 ± 303.9 pg/mL. Strong association was found between plasma sclerostin level and the presence of osteolytic bone disease ($P < 0.001$), [Figure 2].

For statistical purposes patients with stages I and II were included together. Statistically significant association was found between plasma sclerostin levels in patients

Table 2: Radiological findings of MM patients

Radiological findings	Frequency (%)
Osteolytic lesions $\pm$ Osteoporosis $\pm$ Pathological fractures	29 (72.5%)
Osteoporosis only	6 (15%)
No bone involvement	5 (12.5%)
Total	40 (100%)

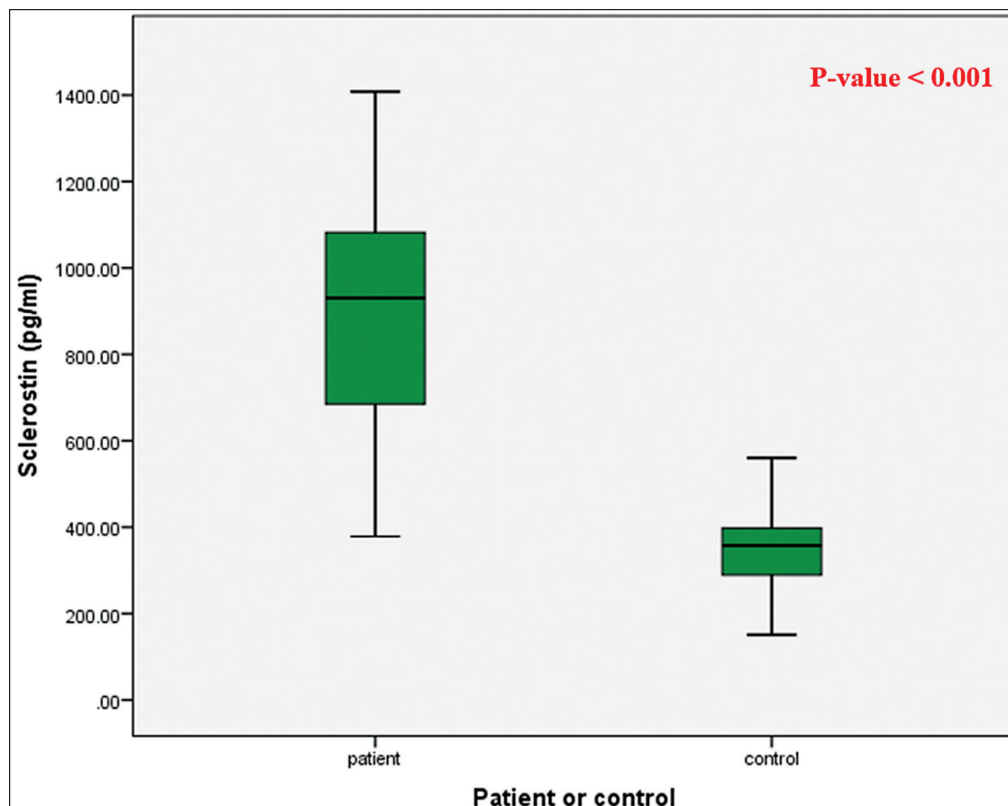


Figure 1: Comparison of sclerostin levels in control group and MM patients

Table 3: Correlation of Sclerostin level with age and laboratory parameters in patients' groups

Parameter	Sclerostin	
	*r	p
Age	0.123	0.277
ANC	0.203	0.282
Hb	-0.077	0.639
Platelets	-0.204	0.207
ESR	0.191	0.237
BM plasma cell%	0.134	0.439
Serum uric acid	0.4	0.018
Serum calcium	0.125	0.443
Serum albumin	-0.148	0.363
Blood urea	0.336	0.034
Serum creatinine	0.549	<0.001
GFR	-0.521	0.001
β2-microglobulin	0.744	<0.001

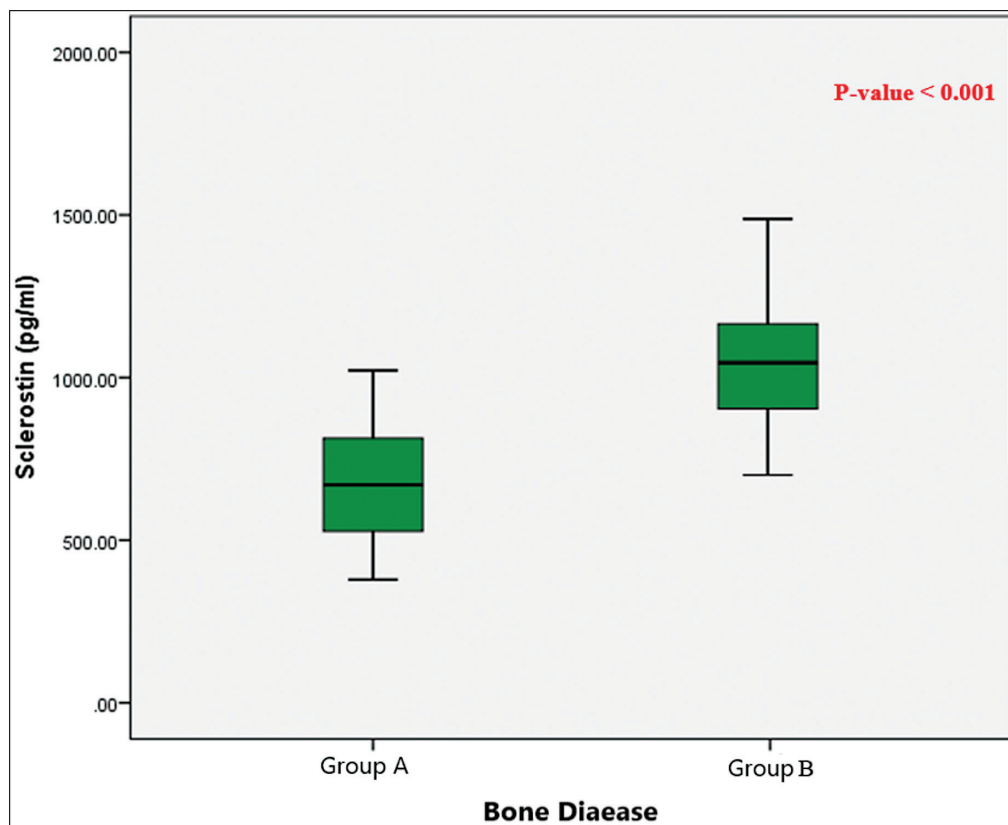
*Spearman rho correlation

with stage III compared to those with stage I and stage II, indicating a significant association between plasma sclerostin level and advanced disease stage ($P = 0.003$), [Table 4].

DISCUSSION

In this study the mean age of newly diagnosed MM patients was comparable to previous local Iraqi studies in which the mean age was around 60 years.^[13,14] In western countries, the reported median age for disease presentation is higher. One American study reported a median age of 70 years and in another Swedish study the median age was 72 years. The plausible elucidations are varied genetic composition and a higher mean age of population in western countries.^[13,14]

A slight female predominance (52.5%) was observed in this study, which was consistent with that reported by other studies.^[15,16]

**Figure 2:** Comparison of sclerostin level between myeloma patients group A and B**Table 4: Sclerostin level in myeloma stages**

Parameter		Stage I, II N=10	Stage III N=30	P-value*
Sclerostin level (pg/mL)	Mean	631.57	957.33	0.003
	SD	190.49	196.19	
	Range	378.53-987.4	623.25-1208.06	

* Mann Whitney test

The frequency of bone pain was comparable to findings of Alwan AF who reported bone pain in 86.9% but higher than that reported by Samuel HU, Qian J *et al.* who observed bone pain in 74% and 52.1% of patients, respectively. Furthermore, pathological fractures were reported in 15% of the newly diagnosed MM patients. This finding was comparable to that reported by other studies.^[17–19]

Another common clinical finding was pallor, finding comparable to other studies done in Iraq.^[13,14,17] Worldwide studies have also concluded that anemia was one of the most common complications in MM but at a lower rate (40% to 60%). Anemia predominance may be attributed to the late presentation of Iraqi patients to hematology clinics since most patients only sought medical attention after they developed backache, bone pain or pathological fractures.^[19–22]

The mean GFR level was comparable to those of Derman *et al.* who reported a mean GFR of 51.5 in non-African American newly diagnosed MM patients and Qian Y. *et al.* who found a baseline GFR <60 in 61% of newly diagnosed MM patients.^[15,23]

The findings of monoclonal M band detected in serum and urine were in agreement with those reported by other studies.^[13,24]

The prevalence of osteolytic bone lesions (72.5%) was a bit higher than that reported by Abdullah MA *et al.*^[14] (68%) but lower than that of Terpos E *et al.*^[25] (78%).

Plasma sclerostin levels were significantly increased in untreated MM patients compared to the control group. A finding consistent with that of Eda H. *et al.*^[26] who found higher levels of sclerostin in MM patients' plasma compared to leukemia patients, and healthy volunteers. Terpos E *et al.*^[25] evaluated circulating sclerostin and found that patients with active myeloma had elevated circulating sclerostin compared to patients with monoclonal gammopathy with undetermined significance and a healthy control group. A similar result was also reported by Wang XT *et al.*^[27] who demonstrated higher plasma sclerostin level compared to control group.

High sclerostin level was associated with a decline in GFR a finding similar to that reported by Morena *et al.* who studied sclerostin level in 241 cases with chronic kidney disease and found that decline in renal function was associated with a significant increase in sclerostin.^[28]

The significant correlation found between sclerostin level, β 2M, blood urea, and serum creatinine is in agreement with that of other studies.^[25,27]

Sclerostin levels in myeloma patients with bone disease is consistent with that reported by other studies illustrating that sclerostin might play an important role in the development and progression of MBD.^[25,27] Moreover, this

finding was supported by *in vitro* studies suggesting that myeloma cells through interactions with bone marrow stromal cells lead to enhanced production of sclerostin that contributes to osteoblast dysfunction and osteoclast activation. Furthermore, another study revealed that the interaction of myeloma cells with osteocytes triggers osteoclastogenesis through increased osteocyte apoptosis and the production of pro-osteoclastogenic cytokines in active myeloma patients.^[29,30]

Terpos E *et al.* hypothesized that advanced myeloma may lead to higher osteocyte apoptosis that release sclerostin which can be detected in the serum. This supports a significant role of sclerostin in the development of bone destruction in myeloma.^[25]

In our study, sclerostin level was associated with advanced disease suggesting that sclerostin levels might reflect the tumor burden. Similar results had been reported by other studies.^[25,27]

The mechanism underlying the increased levels of sclerostin correlated with tumor burden is unclear but some studies suggest that it may be related to the inhibition of bone marrow stromal cell differentiation to osteoblasts by sclerostin, resulting in the generation of factors promoting the growth of myeloma cells, such as interleukin-6. Furthermore, studies have shown that sclerostin is also involved in inducing an increase in the levels of RANKL which may stimulate myeloma cell proliferation.^[27]

CONCLUSIONS

In newly diagnosed MM patients, the plasma sclerostin was significantly high which was positively correlated with increased blood urea, serum uric acid and low GFR. Higher levels of plasma sclerostin were associated with advanced disease stage and with the presence of significant bone disease. No significant correlation was found between plasma sclerostin levels and the clinical or hematological parameters in MM patients.

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Conflicts of interest

There are no conflicts of interest.

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