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Serum sclerostin and sympathetic skin response: relationship with myeloma bone disease

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Abstract

Background: Myeloma bone disease (MBD) is a common complication that significantly contributes to morbidity and mortality in multiple myeloma (MM). Serum sclerostin level and sympathetic activity can affect MBD. The purpose of this study is evaluation of serum sclerostin level and sympathetic activity (using sympathetic skin response "SSR") in MM patients, and studying the relationship between both of them as well as their relationship with MBD. 35 smoldering myeloma patients (group I) and 35 newly diagnosed MM (group II) and 35 controls (group III) were included in the study. All the participants were subjected to complete history taking, and clinical examination. Assessment of serum sclerostin level, SSR, MM stages [by the international staging system (ISS)], MBD grading (according to the Durie–Salmon staging system) were done for all patients within 7 days from the diagnosis.

Results: Undetectable and decreased SSR amplitude are significantly more detected in group I and II (compared with group III). Autonomic manifestations, and loss of SSR is significantly more detected in group II than group I. Autonomic manifestations were absent in group III. SSR amplitude of median and tibial nerves is significantly decreased in group II than group I and III. MBD was detected in all patients of group II. Serum sclerostin and LDH were significantly increased in group II than group I. Group I and II had significantly higher levels of sclerostin when compared with group III. Group II had significantly higher levels of sclerostin and lower levels of ALP in comparison with group I. Serum sclerostin level was correlated positively with LDH and negatively with ALP and SSR amplitude. MBD was significantly affected by ISS stage III, LDH level, SSR affection and serum sclerostin level $\geq$ 0.40 ng/ml. SSR response affection was the most significant risk factor for advanced MBD followed by increased sclerostin level.

Conclusions: Serum sclerostin level was significantly increased and sympathetic activity was significantly decreased in MBD. Loss of the SSR response was the most significant risk factor for advanced MBD followed by increased sclerostin level.

Recommendations: Potentially validating the use of bone-turnover markers in larger studies, in addition to electrophysiological examination of SSR to stratify patients who are at high-risk for progressive MBD, as the use of newer agents with anabolic effects such as anti-sclerostin antibodies have shown potential in repair of MBD. These newer agents could potentially change the treatment landscape in patients with MBD.

Keywords: Sympathetic skin response, Multiple myeloma, Smoldering myeloma, Circulating sclerostin, Myeloma bone disease

Background

Bone marrow contains stem progenitor, and multifunctional differentiated cell types of several different lineages which all work together to maintain a complex

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microenvironment. In healthy bone marrow, these mesenchymal stem cells (MSCs) can differentiate into chondrocytes, adipocytes or osteoblasts [1, 2].

Multiple myeloma (MM) is characterized by clonal bone marrow plasma cells > 10% or biopsy proven plasmacytoma and any one or more of myeloma-defining events such as end-organ damage, other biomarkers of malignancy (including clonal bone marrow plasma cell percentage ≥ 60%; serum involved/uninvolved free light chains ratio > 100; more than one focal lesion ≥ 5 mm in magnetic resonance imaging), or amyloidosis which can be attributed to the plasma cell proliferative disorder [3].

Smoldering multiple myeloma (SMM) is characterized by an M-component > 3 g/dl, bone marrow plasma cell infiltration > 10% and less than 60%. SMM does not show the clinical features of end-organ damage, nor any of the other myeloma-defining events of active MM. All cases of MM evolve through SMM stages, although these are often not clinically evident [3].

Osteolytic bone disease is one of the most common and devastating complications of MM. Sclerostin is a glycoprotein produced by osteocytes that blocks canonical Wingless-type (Wnt) signaling by binding to low-density lipoprotein related protein (LRP) 5/6 coreceptors which is crucial for the osteoblast differentiation and activity, in addition to inhibition of osteoblast-driven bone formation sclerostin also promotes osteoblast apoptosis [4].

Sympathetic nerves participate in both niche-driven blood cancers and niche remodeling by cancer cells [5]. Also, the areas of mineralized bone that receive the greatest mechanical stress and load have the highest metabolic rate and bone turnover. They are the most vascularized and display the highest density of sympathetic and sensory fibers [6].

Neural regulation of the niche and control of hematopoietic stem cell (HSC) export is mediated through the sympathetic nervous system (SNS). β2-adrenoceptors on MSCs can mediate changes in the osteoblast differentiation and bone remodeling [2]. Sympathetic activity is frequently an elusive diagnosis, and specialized testing may be required [7].

Sympathetic skin response (SSR) is a polysynaptic reflex that is activated by a variety of afferent inputs. The final efferent pathway involves pre- and post-ganglionic sympathetic sudomotor fibers and ultimately activation of sweat glands by the sympathetic outflow. Sympathetic derangement evaluated by sympathetic skin response is a reliable noninvasive indicator of autonomic function [8].

There are only few reported cases of MM with autonomic disturbance. Moreover, most of the studies were animal based [9]. We hypothesized that sclerostin level is elevated in MBD, and sympathetic activity is disturbed in MM. This disturbance may be significantly related to sclerostin level and MBD.

The purpose of the current study is evaluation of serum sclerostin level and sympathetic activity (using sympathetic skin response "SSR") in MM patients, and studying the relationship between both of them as well as their relationship with myeloma bone disease (MBD).

Methods

Study design and patients

We have prospectively studied 3 groups (age and sex matched): 35 smoldering myeloma patients comprised group I, 35 newly diagnosed multiple myeloma patients comprised group II and 35 apparently healthy subjects (proved by clinical and laboratory investigations—obtained from dental clinic and not of the patient's relatives) comprised group III.

Patients were eligible when their age was 18 years or older in the absence of other hematologic malignancies, or any clinical condition that could affect autonomic nervous system, like diabetes mellitus, alcohol consumption, addiction, connective tissue disease or amyloidosis. Patients were excluded if they had received drugs that may alter autonomic nervous system in the last 6 months, including bortezomib. Patients with other clinical conditions that may affect bone such as thyroid dysfunction, parathyroid dysfunction and medication that may alter the normal bone turnover during the last 6 months like steroids, were also excluded.

Diagnoses of smoldering myeloma, and multiple myeloma were done according to International Myeloma Working Group criteria [10].

The study was conducted with Ethical Committee approval (ZU-IRB#9177/2-4-2018). Before their participation in the study, all subjects were given informed consent. The study was conducted in the clinical pathology, neurology, rheumatology and rehabilitation and medical oncology departments of Zagazig university Hospitals.

Clinical, laboratory and neurophysiological assessments

All assessments were done within 7 days from the diagnosis. All the participants were subjected to complete history taking, thorough clinical (general and neurological) examination with special attention to the presence of autonomic manifestation such as skin discoloration, change in skin temperature, sweating, change in blood pressure, change in heart rate, dry mouth, constipation or diarrhea. We used the International Staging System (ISS) [10] for assessment of multiple myeloma disease stages. It consists of three stages: Stage 1 means that the level of the protein called beta 2 microglobulin (ß2-M) is less than 3.5 mg per liter (mg/l), the level of albumin in the blood is more than 3.5 g per deciliter (g/dl), normal LDH

level and low risk of cytogenetics. Stage 2 means that the level of ß2-M is between 3.5 and 5.5 mg/l, with any albumin level or the level of ß2-M is less than 3.5 mg/l and the level of albumin is less than 3.5 g/dl, normal LDH with low risk of cytogenetics. Stage 3 means that the level of ß2-M is more than 5.5 mg/l, high LDH level and high risk of cytogenetics.

Myeloma bone disease means the presence of one or more lytic bone lesions on computed tomography or magnetic resonance imaging (more than one focal lesion ≥ 5 mm in magnetic resonance imaging). MBD grading was done according to the Durie–Salmon staging system [11]: group A (patients with no lytic lesions); group B (patients with 1–3 osteolytic lesions), and group C (patients with more than three osteolytic lesions and/or a pathological fracture due to multiple myeloma). We have used the > 3 as cut-off for bone lesions, as advanced bone disease includes more than three lytic lesions.

Blood samples were taken from all subjects and were divided into three tubes:

- The 1st plain tube for total calcium, alkaline phosphatase, vitamin D (cut-off for normal value is ≥ 20 ng/ml), and parathyroid hormone: the total calcium and alkaline phosphatase were measured photometrically on cobas c 311/501 analyzer. Vitamin D and parathyroid hormone were assayed by the electrochemiluminescence immunoassay on cobas e601 immunoassay analyzer.
- The 2nd tube for serum measurement of sclerostin that was done using a sandwich-type enzyme linked immunosorbent assay (ELISA) from Tecomedical (TE 1023-HS, Sissach, Switzerland) and the coefficient of variation for intra-assay was from 3.7 to 4.2% and inter-assay was from 4.3 to 4.8%.
- The 3rd EDTA tube for complete blood count and the 4th routine laboratory data including kidney functions, lactate dehydrogenase (LDH), and β2-microglobulin were also done.

Sympathetic skin response (SSR) was used for evaluation of sympathetic activity. The SSR technique and recordings were based on the procedures described by Shahani and his colleagues [12]. Sympathetic skin response was recorded with surface electrodes and Nihon Kohden electromyographic machine (Neuropack X1, MEB 2300, 6 and 12 channels EMG/EP measuring system, with Neuro-Work-bench software).

The testing room should be light dimmed, and the room temperature should be kept between 22 and 24 °C to avoid any confounding. Skin temperature of the examined limbs remained unchanged (32 ± 0.5 °C) all over the time of the test [13].

Surface disc electrodes were used. The active electrode was placed on the palmar surfaces of the hand above the third metacarpal bones (at 3 cm from the distal end), and the reference electrode was placed on the corresponding area of the dorsum of the examined hand. The ground electrode was placed on the forearm. All participants were examined by stimulation of the median nerve at the wrist ipsilateral to the recording electrode. Also, the active electrode was placed on the palmar surfaces of the foot above the web between first and second metatarsal bones, and the reference electrode was placed on the corresponding area of the dorsum of the examined foot. The ground electrode was placed on the leg. All participants were examined by stimulation of the tibial nerve at the ankle ipsilateral to the recording electrode. Each stimulus is composed of a single electrical pulse (pulse width 0.5 ms). The frequency filters are set low (usually to 0.1–0.5 Hz) due to the low increase of the electrodermal potential caused by the sweat appearance on the skin surface. The amplifiers' sensitivity was 100 μV/division. Also, the sweep speed was set as 1000 ms/D. The stimulus intensity ranged from 10 to 40 mA, and it was delivered at the wrist at an irregular interval (30–35 s). Five trials were recorded from the palmar aspect of the examined hand and foot with the largest amplitude, and shortest latency was taken. The average of the potentials was taken into consideration. To avoid any habituation effect, stimulation was done with randomized intervals and varying intensity. Latency was measured from the onset of the stimulus artifact to the first deflection of the potential from baseline, and the amplitude was measured from peak to peak. Only reproducible responses without any movement artifact that were consistent were selected for analysis because each response can vary somewhat, only the consistent responses with some variation in each subject were selected for analysis. The recorded SSR graphs are analyzed for presence or absence as well as for latency and amplitude of the electrical potential change. A missing SSR may require a second electrical stimulation. Usually, the palmar SSR has a shorter latency, but higher amplitude than the plantar SSR (hands 1.5 s latency, 0.5–1.3 mV amplitude, feet 1.9–2.1 s latency, 0.15–0.8 mV amplitude) [14].

Statistical analysis

The data collected of the current study were statistically analyzed using the Statistical Package of Social Science (SPSS) program for Windows version 24 (Released 2016 by International Business Machines Corporation, USA). Unpaired *T* test, one-way ANOVA or Mann–Whitney test was used to test for differences between the different groups according to type of data. Wilcoxon signed ranks test was used to test for differences within groups.

Kruskal–Wallis test, Spearman correlation test and multiple logistic regression analysis were done.

Results

Clinical characteristics of the individuals included in our study are listed in Table 1. Their gender and ages (median and range/years) were as follows: group I; 20 males and 15 females (65 "36–85"), group II; 18 males/17 females (66 "40–75") and group III; 16 males/19 females (59 "49–73").

There was non-significant difference between patients (group I and II) and controls regarding clinical characteristics ($p > 0.05$). Autonomic manifestations such as skin discoloration, change in skin temperature, sweating, change in blood pressure, change in heart rate, dry mouth, constipation or diarrhea were detected in 17 (48%) multiple myeloma patients, and 8 (23%) smoldering myeloma patients. Autonomic manifestations were significantly more detected in group II than group I. Autonomic manifestations were absent in group III. Comparing groups, I and II versus group III showed that undetectable SSR and decreased SSR amplitude were significantly detected in group I and II (compared versus group III). Loss of SSR was significantly more detected in group II than group I. Sympathetic activity amplitude of median and tibial nerves was significantly decreased in group II than group I ($p = 0.01$, 0.03, respectively) and in group II than group III ($p = 0.02$, 0.02, respectively) (Table 1).

Comparing groups, I versus group II; myeloma bone disease was detected in all patients of group II. Hemoglobin, serum creatinine, serum sclerostin and lactate dehydrogenase were significantly elevated in group II than group I ($p = 0.0005, < 0.0001$, 0.007 and 0.04) (Table 2).

Group I and II had significant higher levels of sclerostin when compared with group III (p 0.02 and 0.01). Group II had significant higher levels of sclerostin level and lower significant level of ALP in comparison with group I (p: 0.03 and 0.04). There were no differences among groups regarding serum levels of vitamin D and PTH (Table 3).

Serum sclerostin level had significant positive correlation with LDH ($p = 0.03$). It correlated negatively with ALP, SSR amplitudes in upper and lower limbs ($p = 0.01$, 0.01 and 0.02) (Table 4).

Doing multivariate analysis showed that advanced MBD was significantly affected by ISS stage 3 ($p = 0.03$), increased LDH level ($p = 0.01$), loss of SSR ($p = 0.02$) and serum sclerostin elevation ≥ 0.40 ng/ml ($p = 0.04$) (Table 5).

Logistic regression analysis showed that loss of SSR response was the most significant risk factor for advanced MBD ($p = 0.001$), followed by increased serum sclerostin level ≥ 0.40 ng/ml (0.01) (Table 6).

Table 1 Demographic data, autonomic manifestations and electrodiagnostic data of the studied groups

		Smoldering myeloma Group I ($N = 35$)	Multiple myeloma patients Group II ($N = 35$)	p^+	Controls Group III ($N = 35$)	p^*
Gender (male/female)		20 (57%)/15 (43%)	18 (51%)/17 (49%)	0.6	16 (46%)/19 (54%)	0.36, 0.68
Age: median (range)		65 (36–85)	66 (40–75)	0.3	59 (49–73)	0.21, 0.16
Autonomic manifestations		8 (23%)	17 (48%)$^+$	0.03	–	–
Undetectable SSR		6 (17%)*	15 (42%)*$^+$	0.02	3 (6%)	0.01, 0.01
SSR amplitude/μv	UL (median n. stimulation)	1300	500*+	0.01	2100	0.1, 0.02
	LL (tibial n. stimulation)	900	300*$^+$	0.03	1600	0.4, 0.02

SSR sympathetic skin response, *UL* upper limb, *LL* lower limb, *n* nerve

*Significant comparing either group I or II versus group III, $^+$significant comparing group II versus group I

Table 2 Radiological, and laboratory data of the smoldering myeloma (group I) and multiple myeloma (group II) patients

	Group I ($N = 35$)	Group II ($N = 35$)	p value
Hemoglobin < 10 g/l	2 (6%)	15 (42%)*	0.0005
Serum creatinine ≥ 2 mg/dl	1 (3%)	17 (49%)*	< 0.0001
Albumin < 3.5 gm/dl	19 (54%)	18 (51%)	0.8
Serum β2 microglobulin > 3 mg/l	18 (51%)	21 (60%)	0.4
Lactate dehydrogenase > 240 U/l	7 (20%)	15 (42%)*	0.04
Serum sclerostin (ng/ml)	0.52 (±0.38)	0.77 (±0.37)*	0.007
Myeloma bone disease	–	35 (100%)	

*Significant comparing group I group II

Table 3 Comparing bone remodeling parameters and serum sclerostin levels among all groups (I and II and III)

Parameter			ALP (U/l)	Vitamin D (ng/ml)	PTH (pg /ml)	Serum sclerostin (ng/ml)
Group I			20.3 (± 11.7)	16.7 (± 10.2)	30.2 (± 6.1)	0.52 (± 0.38)
Group II			14.7 (± 11.7)	19.3 (± 5.2)	31.6 (± 2.9)	0.77 (± 0.37)
Group III			18.3 (± 11.2)	20.1 (± 9.2)	31.9 (± 3.7)	0.41 (± 0.36)
P	Group I versus III		0.47	0.15	0.16	0.02*
P	Group II vs	group I	0.04^{+}	0.18	0.22	0.03^{+}
		Group III	0.19	0.65	0.71	0.01*

ALP bone-alkaline phosphatase, *PTH* parathyroid hormone, *vs* versus

*Significant comparing either group I or II versus group III, $^{+}$significant comparing group II versus group I

Table 4 Correlation between serum sclerostin level and different parameters

Parameter		Laboratory		SSR amplitude/uv	
		ALP	LDH	Upper limbs (median nerve)	Lower limbs (tibial nerve)
Serum sclerostin	*p* value	0.01*	0.03*	0.01*	0.02
	R	− 0.43	+ 0.55	− 0.42	− 0.55

ALP bone-alkaline phosphatase, *LDH* lactate dehydrogenase, *uv* microvolt

*Significant

Discussion

Sclerostin has been implicated in myeloma bone disease (MBD) [4]. To date little is known about the significance of sympathetic signaling in multiple myeloma (MM) [9]. We hypothesized that sclerostin level is elevated in MBD, and sympathetic activity is disturbed in multiple myeloma. This disturbance may be significantly related to sclerostin level and MBD.

The purpose of the current study is evaluation of serum sclerostin level and sympathetic activity (using sympathetic skin response "SSR") in multiple myeloma patients, and studying the relationship between both of them as well as their relationship with myeloma bone disease.

Autonomic manifestations such as skin discoloration, change in skin temperature, sweating, change in blood pressure, change in heart rate, dry mouth, constipation or diarrhea were significantly more detected in group II than group I. Autonomic manifestations were absent in group III. Undetectable SSR and decreased SSR amplitude were significantly detected in group I and II compared versus group III. Loss of SSR was significantly more detected in group II than group I. Sympathetic activity amplitude of median and tibial nerves was significantly decreased in group II than group I and III.

This finding met with the findings of Wolf and colleagues [15] found that sympathetic dysfunctions slowly

Table 5 Multivariate analyses between different risk factors and advanced myeloma bone disease (MBD- grade 3) in multiple myeloma patients (group II)

Variables	MBD (35)		OR [95% CI]	*p* value
	Advanced (20)	Not advanced (15)		
Sex				
Females (16)	9	7	5.5 [0.2–8.7]	0.5
Males (19)	11	8		
Age at diagnosis				
> 60 years (14)	8	6	3.9 [0.12–8.97]	0.6
≤ 60 years (21)	12	9		
ISS stages				
3 (22)	13	9	9.9 [10.2–13.3]	0.03*
1 and 2 (13)	7	6		
LDH				
Elevated (23)	15	8	6.1 [11.2–13.3]	0.01*
Not elevated (12)	5	7		
SSR				
Undetectable (15)	14	1	5.5 [11.9–22.1]	0.02*
Detectable (20)	6	14		
Serum sclerostin				
≥ 0.40 ng/ml (23)	18	5	5.9 [13.9–14.67]	0.04*
< 0.40 ng/ml (12)	2	10		

OR odds ratio, *CI* confidence interval, *ISS* International Staging System, *MBD* myeloma bone disease, *SSR* sympathetic skin response, *LDH* lactate dehydrogenase

*Significant

Table 6 Logistic regression analysis declaring the significant risk factors on advanced myeloma bone disease

Variables	OR [95% CI]	*p* value
Undetectable SSR	2.6 [8.8–12.6]	0.001*
Increased serum sclerostin level ≥ 0.40 ng/ml	3.5 [10.3–11.1]	0.01*
ISS stages 3	5.5 [11.5–16.2]	0.5

OR odds ratio, *CI* confidence interval, *SSR* sympathetic skin response, *ISS* International Staging System

*Significant

and steadily progressed and did not show any improvement. After 10 years of slowly progressive smoldering myeloma, the patient needed alpha 1 adrenoceptor agonist therapy with midodrine (2.5 mg three times daily) to get up from bed and to walk with mechanical support. The ability to sweat had ceased almost completely. Also, Zhang [16] stated that clinical manifestations in multiple myeloma patients are aggravated by decreased sympathetic activity.

Myeloma bone disease was detected in all patients of group II. Hemoglobin, serum creatinine, serum sclerostin and LDH were significantly affected in group II than group I. Group I and II had significant higher levels of sclerostin when compared with group III. Group II had significant higher levels of sclerostin and lower significant level of ALP in comparison with group I. There were no differences among groups regarding serum levels of vitamin D or PTH.

Hand in hand with our findings; Jakob and colleagues [17] found that sclerostin was significantly higher in multiple myeloma patients when compared with the normal controls. Also, Goranova-Marinova and colleagues [18] found a serious increase of the sclerostin in multiple myeloma. They stated that sclerostin induces ligand of receptor activator of nuclear factor-kappa B (RANKL) expression by the bone marrow stromal cells and osteoblasts. Moreover, sclerostin inhibits the activity of osteoblasts. Myeloma cells participate in this process and probably produce certain amounts of RANKL themselves. Moreover, myeloma cells, internalize degradation of osteoprotegerin (OPG).

This could be explained by the findings of Terpos and colleagues, [19] who stated that OPG is high in early clinical stages and in patients with minimal bone lesions because, osteoblast function was still coupled to the intensified osteoclast function. Its decrease as the disease evolves was a result of the suppressive effects of sclerostin.

In the current study, serum sclerostin level had significant positive correlation with LDH. It correlated negatively with ALP. That met with the findings of Terpos and colleagues, [4] who found that elevated sclerostin correlated significantly with reduced bone formation in multiple myeloma as assessed by the strong negative correlation with ALP (a sensitive bone formation marker). Also, they found that it had a significant positive correlation with disease progression and increased LDH level.

Surprisingly, we found that there was a significant negative correlation between the increment of serum sclerostin level and the decreased SSR amplitude in upper and lower limbs.

Doing multivariate analysis; advanced MBD was significantly related to ISS stage3, increased LDH level, loss of SSR and serum sclerostin elevation ≥ 0.40 ng/ml. Logistic regression analysis showed that loss of SSR response was the most significant risk factor for advanced MBD followed by increased serum sclerostin level.

Our data suggest that the disastrous effects of the sympathetic dysfunction on MBD were augmented by the elevation of serum sclerostin level.

Corr and colleagues [20] supported the findings of our present study. They stated that high sympathetic tone caused by chronic stress promotes MBD through increased osteocyte secretion of sclerostin. It is well known that sclerostin inhibits the osteogenic wingless-type (Wnt)/β-catenin pathway in mesenchymal stem cells (MSCs) impeding their ability to differentiate into mineralizing osteoblasts (OBs). In addition to its antianabolic effect, sclerostin promotes the catabolic activity of osteoclast through expression of RANKL, and decreasing the expression of OPG. Sclerostin was overproduced by plasma cells from multiple myeloma patients [21].

In Rogers and Eastell study [22], they did not detect a relationship between sympathetic activity and the RANKL/OPG cytokine system. There may be several reasons for this occurrence. First, the levels of these cytokines in serum may not mirror their levels or activity in the bone microenvironment. Second, they did not correlate their findings with sclerostin and its effect on RANKL/OPG cytokine system.

Fairfield and colleagues [1] hypothesized that there was a shift in allocation of MSCs toward adipocyte formation and away from osteoblastogenesis that is mediated by sclerostin so sclerostin signaling may induce adipogenesis. Anti-sclerostin therapy can be used to reduce the action of sclerostin, leading to increased Wnt signaling and subsequent osteoblastogenesis.

Also, data of Takeda and colleagues [23] suggested that the adipogenic differentiation of skeletal stem cells may require leptin signaling. Also, adipose tissue conveys information to bone indirectly via leptin signaling in the sympathetic nervous system. These signals appear to be

largely anti-osteogenic and are likely β-adrenergic receptor dependent.

Sclerostin has been implicated in MBD, inhibitors of sclerostin are drug candidates against myeloma-induced bone disease. Routine SSR examination will be helpful as it reflects myeloma bone disease especially when MBD is advanced, in addition to its correlation with the elevated sclerostin level. Thus, hematologist must be aware of the possibility of sympathetic decreased activity that maybe hidden in such a case, which may be treatable by specific treatment regimens in addition to that are typically used for multiple myeloma.

Limitations of the study it has been reported that patients aged 50 years or more tend to have no recordable SSR. Also, a large inter-individual variability in SSR has been described [24] Thus, SSR interpretation should be performed together with other sudomotor function tests.

Conclusions

Decreased sympathetic activity was significantly correlated to sclerostin elevation, which significantly dampens osteoblastic activity and eventually myeloma bone disease.

Recommendations

Potentially validating the use of bone-turnover markers in larger studies, in addition to electrophysiological examination of SSR to stratify patients who are at high-risk for progressive MBD, as the use of newer agents with anabolic effects, such as anti-sclerostin antibodies have shown potential in repair of MBD. These newer agents could potentially change the treatment landscape in patients with MBD.

Abbreviations

MM: Multiple myeloma; SMM: Smoldering multiple myeloma; MBD: Myeloma bone disease; MSCs: Mesenchymal stem cells; HSC: Hematopoietic stem cell; SNS: Sympathetic nervous system; SSR: Sympathetic skin response; RANKL: Ligand of receptor activator of nuclear factor-kappa B; Wnt: Wingless-type; LRP: Low-density lipoprotein related protein; ISS: International Staging System; B2-M: B2 microglobulin; ELISA: Enzyme linked immunosorbent assay; LDH: Lactate dehydrogenase; ALP: Alkaline phosphatase; PTH: Parathyroid hormone; UL: Upper limb; LL: Lower limb; n: Nerve; OR: Odds ratio; CI: Confidence interval; OBs: Osteoblasts.

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Author contributions

AO, RN, AW, GN and ME carried out the work. All authors contributed equally to the conception, design, writing, drafting, revising the article critically for important intellectual content, and all authors approved the final version to be published in the journal. All authors read and approved the final manuscript.

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Availability of data and materials

From the corresponding author.

Declarations

Ethics approval and consent to participate

The study was approved from the institute research board of Faculty of Medicine, Zagazig University, Egypt (ZU-IRB#9177/2-4-2018). A written informed consent was obtained from all the participants or their responsible relatives after informing them about the study rationale and their right to withdraw from the study at any time without any consequences.

Consent for publication

All participants had signed an informed consent to participate and for the data to be published.

Competing interests

The authors declared following the potential competing of interest with respect to the research, authorship, and publication of this article.

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