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# Serum sclerostin in rheumatoid-induced osteoporosis



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## Abstract

**Background:** Rheumatoid arthritis (RA) is characterized by presence of localized and generalized osteoporosis. The mechanism of decreased bone mass is complex and multifactorial, a possible mechanism behind increased bone loss in RA is upregulation of sclerostin. The aim of this work was to evaluate serum sclerostin level in RA patients and its relation with bone mineral density (BMD) and disease activity.

**Results:** Serum sclerostin level in RA patients was significantly higher than the controls ( $p < 0.001$ ). Osteopenia and osteoporosis were more prevalent in RA patients (22.5% and 7.5% respectively) compared to controls (15% and 2.5% respectively) ( $p = 0.006$ ). Serum sclerostin level was significantly correlated with tender joint count ( $p = 0.014$ ), swollen joint count ( $p = 0.036$ ), erythrocytes sedimentation rate ( $p = 0.010$ ), C reactive protein serum level ( $p = 0.025$ ), disease activity score (DAS) 28-ESR ( $p = 0.018$ ), DAS28-CRP ( $p = 0.005$ ), and radiological modified Sharp erosion score ( $p = 0.049$ ). The correlation of serum sclerostin level in RA patients with BMD and with T-score in all sites revealed an inverse relationship with  $p$  values insignificant.

**Conclusion:** Serum sclerostin is a major player in bone metabolism as a negative regulator of bone growth through inhibition of Wnt signaling that is largely influenced by the disease activity. Controlling the disease activity is a major factor for prevention of local as well as generalized osteoporosis and is essential for the reparative local and systemic bone health.

**Keywords:** Rheumatoid arthritis, Bone mineral density, Osteoporosis, Sclerostin

## Background

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease characterized by chronic synovial inflammation with subsequent joint destruction and deformity [1]. Osteoporosis is more common in RA patients than in the general population [2]; with estimates revealed that approximately 32% and 26% of patients with longstanding RA had evidence of osteoporosis in lumbar spine and femoral neck respectively, almost twofold of the prevalence found in matched controls [3–5]. Interestingly, osteoporosis was observed in RA patients who were never exposed to corticosteroids, indicating that RA by itself is a significant risk factor for accelerated bone loss [6].

Sclerostin, encoded by SOST gene, is a glycoprotein secreted by osteocytes [7]. Sclerostin is upregulated during inflammation, interacts with low-density lipoprotein receptor-related protein 5/6 (LRP5/6), and displaces Wnt/ $\beta$ -catenin proteins, hence, inhibits osteoblasts differentiation and proliferation [8, 9]. Provided that RA is characterized by an increased rate of localized and generalized osteoporosis, it is hypothesized that the inflammatory background of the disease may contribute to the upregulation of sclerostin resulting in increased bone loss in RA.

However, studies investigated the association of sclerostin with RA had emerged conflicting results. For example, serum sclerostin levels had been reported to be significantly higher [10] or not statistically different [11] than the matched controls. Moreover, studies investigated the relationship between the sclerostin and bone

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loss in RA revealed controversial results as one study had demonstrated that elevated serum sclerostin levels in RA were not associated with bone loss [12] meanwhile another study observed that sclerostin-neutralizing antibodies had prevented or decreased rate of bone mass loss in RA murine models [13]. Review of literature of some Egyptian studies done in psoriatic arthritis (PsA) and ankylosing spondylitis revealed that Sclerostin expression is impaired in early ankylosing spondylitis and was linked to disease activity [14], also it has been found that there is a significant role of sclerostin in the development of inflammation-associated bone damage in PsA [15].

In view of these conflicting data, the aim of this work is to evaluate serum sclerostin level in RA patients and its correlation with bone mineral density (BMD) and disease activity.

## Methods

The present study included 40 RA patients recruited from the outpatient clinic of Rheumatology and Rehabilitation Department and 40 age- and sex-matched apparently healthy controls. The study was conducted in the period from June 2016 to January 2018. All patients fulfilled the 2010 American College of Rheumatology/European League against Rheumatism classification criteria for RA [16]. Prior to inclusion, all participants were adequately informed about study aim and procedures in addition to be provided an informed written consent. The study was approved by the local ethics committee.

Subjects with other autoimmune diseases, secondary causes of osteoporosis (such as diabetes, celiac disease, and thyroid disease), vitamin D deficiency, chronic liver or kidney diseases, and those who were on medications that possibly alter BMD (e.g., estrogen, steroids, calcitonin, bisphosphonates, anticonvulsants, and thyroxin) were excluded from the study.

## Clinical assessment

All participants enrolled in the study were subjected to full history taking and thorough clinical examination. The medical records of the RA patients were reviewed. Demographic characteristics including age, gender, body mass index (BMI) were obtained from all participants. History taking for RA patients included recording of duration of RA, medications and history suggestive of other autoimmune disorders. Clinical evaluation included the 28 tender (TJC) and swollen joint count (SJC), joint pain assessment on 100 mm visual analog scale (VAS-pain), assessment of functional disability using the health assessment questionnaire–disability index (HAQ-DI) score [17]. RA activity was assessed using the disease activity score 28 (DAS28) [18].

## Laboratory investigations

Venous blood samples were withdrawn from all participants for the determination of serum sclerostin using enzyme-linked immunosorbent assay (ELISA) (TECO Medical®, USA) following the manufacturer protocol. In RA patients, rheumatoid factor (RF) was measured by immuno-turbidimetry using Cobas Integra RFII (Roche Diagnostics GmbH, Mannheim, Germany), and serum anti-cyclic citrullinated peptide (anti-CCP) antibodies were measured by ELISA kits (DIASSTAT Axis-Shield, Dundee, UK) following the instructions of the manufacturer. RF values > 15 IU/mL and ACPA values > 20 IU/mL were considered positive [19, 20]. In addition, ESR by the Westergren method and C reactive protein (CRP) were assessed in RA patients.

## Determination of bone mineral density

For measurement of the BMD, the dual-energy X-ray absorptiometry (DEXA) scanning was done for all participants, using the GE Lunar Prodigy Primo Bone Densitometer, General Electric. All DEXA scans were performed by the same operator. The BMD values were presented as g/cm<sup>2</sup>. Cutoffs of T-score were determined based on definitions of the World Health Organization [21].

## Plain radiography

Plain radiographs for hands, wrists, and feet were performed for all patients. Radiological scoring was performed based on the modified Sharp erosion score [22].

## Statistical analysis

All statistical calculations were done through the SPSS version 20.0 statistic software. All continuous data were normally distributed and were presented in mean ± SD. Categorical data were presented in number and percentage. The comparisons were performed using independent sample Student's *t* test for comparison between two variables with continuous data. Chi-square test was used for comparison of variables including categorical data. The 95% confidence interval of mean difference for sclerostin serum level between patients and controls was calculated. Correlation coefficient test was used to explore the relationship between two continuous variables. Statistical significance was set at  $p \leq 0.05$ .

## Results

### General characteristics of patients and controls

As shown in Table 1, no significant difference is found between the RA group and the control group. Table 2 demonstrates the clinical, treatment, laboratory, and radiographic findings of RA patients.

**Table 1** The general characteristics of the RA patients and the controls

	RA group	Control group	P	S
Age (years)	46.7 ± 13.6	45.3 ± 12.2	0.629 <sup>#</sup>	Insignificant
Females (n, %)	33, 82.5%	31, 77.5%	0.576*	Insignificant
Post-menopausal females (n, %)	16/40 (40%)	12/40 (30%)	0.431*	Insignificant
BMI (kg/m <sup>2</sup> )	26.9 ± 2.6	26.8 ± 2.7	0.878 <sup>#</sup>	Insignificant
Family history of osteoporosis (n, %)	6/40 (15%)	4/40 (10%)	0.449*	Insignificant

\*X<sup>2</sup> value, chi-square test<sup>#</sup>t value, Student t test

### DEXA findings and serum sclerostin level in patients and controls

The BMD at the lumbar spine region, neck of femur, and wrist were significantly lower in RA patients than controls;  $p = 0.016$ ,  $p = 0.020$ , and  $p = 0.007$  respectively. In addition, T-score of RA patients at the lumbar spine, neck of femur, and wrist were significantly lower than controls;  $p = 0.019$ ,  $p < 0.001$ , and  $p = 0.007$  respectively (Table 3).

Serum sclerostin level in RA patients ranged between 0.37 and 0.54 ng/ml with a mean of  $0.46 \pm 0.05$  ng/ml meanwhile serum sclerostin level in controls ranged between 0.27 and 0.50 ng/ml with a mean of  $0.37 \pm 0.06$  ng/ml. This difference was significant ( $p < 0.001$ ) (Table 3).

**Table 2** The clinical, laboratory, radiographic, and treatment parameters of RA patients

	Descriptive Mean ± SD	Frequency	
		No	%
Duration of RA (years)	9.8 ± 4.4		
TJC	8.4 ± 2.1		
SJC	7.0 ± 2.0		
VAS-pain (mm)	50.9 ± 7.2		
DAS28-ESR	3.5 ± 1.3		
DAS28-CRP	2.9 ± 0.9		
HAQ-DI	1.8 ± 0.7		
ESR (mm)	51.3 ± 18.4		
CRP (mg/dl)	6.4 ± 3.8		
RF + ve (n, %)		34	85%
Anti-CCP + ve (n, %)		25	62.5%
Modified Sharp X-ray score	79.6 ± 45.8		
MTX (n, %)		32	80.0
LEF (n, %)		15	37.5
HCQ (n, %)		12	30.0

anti-CCP anti-cyclic citrullinated peptide, CRP c-reactive protein, DAS disease activity score, ESR erythrocyte sedimentation rate, HAQ-DI health assessment questionnaire-disability index, HCQ hydroxychloroquine, LEF leflunomide, MTX methotrexate, RA rheumatoid arthritis, RF rheumatoid factor, SWJ swollen joint count, TJC tender joint count, VAS visual analog scale

In RA patients, 22.5% and 7.5% had osteopenia and osteoporosis respectively compared to 15% and 2.5% of controls had osteopenia and osteoporosis respectively. This difference was significant ( $p = 0.006$ ) (Fig. 1).

### Relationship of serum sclerostin level with clinical and laboratory findings in the patients

No significant association was observed between sclerostin serum level and sex, postmenopausal state, family history of osteoporosis, medications intake, RF positivity, nor anti-CCP positivity in RA patients (Table 4). No significant correlation was observed between serum sclerostin and age, BMI, duration of RA, duration of morning stiffness, HAQ-DI, or VAS-pain in RA patients as well (Table 5).

On the other hand, serum sclerostin level was significantly correlated with TJC ( $p = 0.014$ ), SJC ( $p = 0.036$ ), ESR ( $p = 0.010$ ), CRP serum level ( $p = 0.025$ ), DAS28-ESR ( $p = 0.018$ ), DAS28-CRP ( $p = 0.005$ ). The correlation of serum sclerostin level in RA patients with the BMD and with T-score in all sites revealed an inverse relationship, however, with  $p$  values approaching but not reaching threshold of significance. Serum sclerostin level was significantly correlated with radiological modified Sharp erosion score ( $p = 0.049$ ) (Table 5).

### Discussion

The main findings of this study were (a) RA patients had significantly higher serum sclerostin level than controls; (b) serum sclerostin level in RA patients showed an inverse relationship with the BMD and with T-score in all sites, however, with  $p$  values approaching but not reaching borderline of significance; (c) serum sclerostin level was significantly correlated with parameters with disease activity in RA patients; (d) serum sclerostin is significantly correlated with the modified Sharp X-ray score of joint damage in RA patients.

Prevalence of osteoporosis in RA patients varied greatly among studies. The previously reported prevalence of osteoporosis in RA patients was 22.0% [23], 25.0% [24], 30.0% [25, 26], 32.4% [27], 40.4% [28] while in one study it was as high as 79.8% [29]. In patients

**Table 3** Comparison of the DEXA findings and serum sclerostin level between the RA patients and the controls

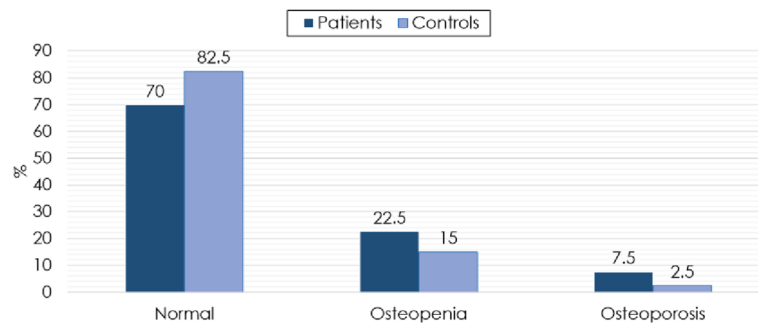
	RA group	Control group	P	S
Bone mineral density (gm/cm <sup>2</sup> )				
Lumbar spine				
Range	0.630-1.160	0.700-1.290		
Mean ± SD	0.869 ± 0.167	0.966 ± 0.183	0.016	Significant
Neck of the femur				
Range	0.580-1.100	0.640-1.210		
Mean ± SD	0.825 ± 0.147	0.908 ± 0.162	0.020	Significant
Wrist				
Range	0.440-1.060	0.530-1.270		
Mean ± SD	0.731 ± 0.213	0.878 ± 0.213	0.007	Significant
T-score				
Lumbar spine				
Range	-4.7--0.6	-3.0--1.0		
Mean ± SD	-2.6 ± 1.2	-2.1 ± 0.7	0.019	Significant
Neck of the femur				
Range	-4.7--0.5	-3.0--1.0		Highly
Mean ± SD	-2.7 ± 1.3	-1.9 ± 0.7	< 0.001	Significant
Wrist				
Range	-4.7--0.5	-2.9--1.0		
Mean ± SD	-2.6 ± 1.2	-1.9 ± 0.6	0.007	Significant
Serum sclerostin level (ng/ml)				
Range	0.37-0.54	0.27-0.50		Highly
Mean ± SD	0.46 ± 0.05	0.37 ± 0.06	< 0.001	Significant

with recent-onset RA (< 6 months duration), osteoporosis was found in 25.0% of the patients [30]. The findings of this study supported the fact that RA patients had significantly lower BMD than healthy controls. In the present study, 30% of RA patients had low BMD (22.5% had osteoporosis and 7.5% had osteopenia).

A major finding of this study is that RA patients had a significantly higher sclerostin serum level than the controls. This finding comes in agreement with the findings

of several previous studies [28, 29]. In Egypt, El-Bakry et al. [13] enrolled 31 RA patients (3 males and 28 females) and 10 healthy controls and reported significantly higher median serum sclerostin in RA patients than in controls a finding that is consistent with the findings of the present study.

In contrast, other studies reported no difference of serum sclerostin level between RA patients and controls [12, 31]. This discrepancy can be attributed to the

**Fig. 1** The frequency of osteopenia and osteoporosis in RA patients and controls

**Table 4** The association of sclerostin serum level with sex, menopausal state, family history, drug intake, RF status, and anti-CCP status of RA patients

	Serum sclerostin level (ng/ml) (mean $\pm$ SD)		<i>t</i> test [ <i>P</i> ]
	Females: 0.45 $\pm$ 0.05	Males: 0.48 $\pm$ 0.04	
Sex			0.146
Postmenopausal	No: 0.44 $\pm$ 0.05	Yes: 0.47 $\pm$ 0.05	0.073
Family history of osteoporosis	No: 0.45 $\pm$ 0.05	Yes: 0.48 $\pm$ 0.05	0.183
MTX	No: 0.45 $\pm$ 0.05	Yes: 0.47 $\pm$ 0.05	0.476
LEF	No: 0.47 $\pm$ 0.05	Yes: 0.45 $\pm$ 0.05	0.273
HCQ	No: 0.46 $\pm$ 0.05	Yes: 0.47 $\pm$ 0.06	0.933
RF	-ve: 0.45 $\pm$ 0.05	+ve: 0.48 $\pm$ 0.05	0.183
Anti-CCP	-ve: 0.45 $\pm$ 0.04	+ve: 0.48 $\pm$ 0.06	0.094

In this table, for example in postmenopausal line, no means no postmenopausal state while yes means postmenopausal state and so on  
*anti-CCP* anti-cyclic citrullinated peptide, *HCQ* hydroxychloroquine, *LEF* leflunomide, *MTX* methotrexate, *RA* rheumatoid arthritis, *RF* rheumatoid factor

characteristics of the RA patients included in these two studies as most of the patients were in clinical remission or had low disease activity which indicates a very low degree of inflammation. Sclerostin expression is upregulated by proinflammatory cytokines during inflammation [9]. Sclerostin serum level depends on genetic factors,

**Table 5** Correlation of the sclerostin serum level with age, BMI, and RA related features

	<i>r</i>	<i>P</i>
Age	0.104	0.523
BMI	0.051	0.754
Duration of RA	0.076	0.640
Duration of morning stiffness	0.098	0.546
TJC	0.375	0.014
SJC	0.333	0.036
VAS-pain	0.114	0.483
HAQ-DI	0.255	0.113
ESR	0.404	0.010
CRP	0.354	0.025
DAS28-ESR	0.371	0.018
DAS28-CRP	0.438	0.005
Modified Sharp X-ray score	0.314	0.049
<b>BMD (gm/cm<sup>2</sup>)</b>		
Lumbar spine	-0.301	0.059
Neck of the femur	-0.299	0.061
Wrist	-0.297	0.063
<b>T-score</b>		
Lumbar spine	-0.305	0.056
Neck of the femur	-0.302	0.058
Wrist	-0.290	0.069

*CRP* c-reactive protein, *DAS* disease activity score, *ESR* erythrocyte sedimentation rate, *HAQ-DI* health assessment questionnaire-disability index, *RA* rheumatoid arthritis, *SWJ* swollen joint count, *TJC* tender joint count, *VAS* visual analog scale

age, sex, adiposity, kidney function, and presence of diabetes mellitus which may account for the discrepancy of the results among the studies [32].

Mehaney et al. [33] studied 40 RA Egyptian patients (12 males and 28 females) with an average age of 48.9  $\pm$  11.6 years and 40 healthy controls and found no significant difference of serum sclerostin level between RA patients compared to controls. This difference may be explained by the differences in the study population as > 62% of the females in the control group in their study were postmenopausal compared to 38.7% in our study.

In the current study, no association had been found between sclerostin serum level with age, sex, or menopausal state. These findings were consistent with results of previous studies [33–36].

Regarding the association between serum sclerostin concentration and RA activity indices, the previous studies revealed conflicting results. The present study showed that serum sclerostin level was significantly correlated with indices of disease activity, which comes in agreement with findings of a previous study on Egyptian patients [37]. Moreover, Brabnikova-Maresova et al. [38] reported that serum sclerostin level is significantly correlated with TJC, CRP, and DAS in juvenile patients with RA. The authors of that study concluded that the association between RA activity indices and serum sclerostin levels indicate inhibition of new bone formation during active inflammation process in juvenile idiopathic arthritis patients. Conversely, El-Bakry et al. [13] found that serum sclerostin level was significantly correlated with TJC but inversely correlated with CRP and DAS.

In the present study, serum sclerostin level showed a significant correlation with the radiological score. El-Bakry et al. [13] and Ibrahim et al. [37] reported significant positive correlation between serum sclerostin and modified Larsen score while Eissa et al. [11]. and Mehaney et al. [34] reported no significant correlation between serum sclerostin and radiological grading. This

discrepancy can be explained by the different radiological scores chosen. The correlation between the serum sclerostin level and erosion score seems reasonable. Impaired repair of bone erosion in RA can be attributed to mechanisms that inhibit new bone formation. Upregulation of sclerostin, the Wnt antagonist, is enhanced during inflammation leading to suppression of repair of bone erosions [39]. Blocking of Wnt antagonists by sclerostin may induce repair or even healing of bone erosions [12].

Several studies assessed the relationship between serum sclerostin level and BMD and the T-score at lumbar spine and at the neck of femur had found conflicting results. In one hand, Mehaney et al. [33] found that although the serum sclerostin level was higher in RA patients with low BMD in comparison to those with normal BMD, these differences were statistically insignificant. On the other hand, other studies found that serum sclerostin is inversely correlated with BMD in healthy and osteoporotic women [40, 41]. Moreover, it was previously reported that sclerostin serum level is positively correlated with BMD at the lumbar spine [31] and at the neck of the femur [38]. In the present study, serum sclerostin level in RA patients had an inverse relationship with the BMD and with T-score in all sites with *p* values approaching but did not reach threshold of significance, in agreement with the results of Mehaney et al. [33].

In two studies by Ardawi et al. [40, 41], who observed an inverse significant correlation between the serum sclerostin level and the BMD, all enrolled women were pre- and post-menopausal healthy (non-RA) women in one study and in the other study all enrolled women were postmenopausal which may account for the discrepancy from the current study. On the other hand, the positive association between BMD and serum sclerostin is difficult to explain, however, Paccou et al. [31] suggested that the sclerostin level may simply reflect the bone mass and the number of active osteocytes.

More studies on sclerostin, in larger RA population, are required for better discrimination of role of sclerostin in patients with RA. In addition, it will be necessary to determine whether anti-sclerostin antibodies could slow the progression of bone mineral loss in RA patients.

## Conclusion

Serum sclerostin is a major player in bone metabolism as a negative regulator of bone growth through inhibition of Wnt signaling that is largely influenced by the disease activity. Controlling the disease activity is a major factor for prevention of local as well as generalized osteoporosis and is essential for the reparative local and systemic bone health. More follow-up longitudinal

studies are recommended to detect the effect of control of disease activity on serum sclerostin and the validity of this serum marker to reflect bone health in RA patients.

## Abbreviations

Anti-CCP: Serum anti-cyclic citrullinated peptide; BMD: Bone mineral density; BMI: Body mass index; CRP: C reactive protein; DAS: Disease activity score; DEXA: Dual-energy X-ray absorptiometry; ELISA: Enzyme-linked immunosorbent assay; HAQ-DI: Health assessment questionnaire–disability index; LRP5/6: Lipoprotein receptor-related protein 5/6; PsA: Psoriatic arthritis; RA: Rheumatoid arthritis; RF: Rheumatoid factor; SJC: Swollen joint count; TJC: Tender joint count

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## Authors' contributions

OG analyzed and interpreted the patients' data, contributed in performing statistical analysis of the results and major contribution in writing manuscript. AH contributed in analyzing and interpreting of patients' data and performing statistical analysis. RE was responsible for performing all laboratory tests present in the study. AE contributed in writing the manuscript. All authors read and approved the final manuscript.

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## Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Ethics approval and consent to participate

The research was approved by Institutional Research Board (IRB) of Mansoura University with code number: MS/16.03.53 by date: 22/3/2016 and the written consent was obtained from all participants and approved by IRB.

## Consent for publication

Not applicable in this study as there are no personal details.

## Competing interests

The authors declare that they have no competing interests.

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