

# Study of serum sclerostin levels in association to enthesal ultrasonography in Egyptian psoriatic arthritis patients

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## Introduction

Serum sclerostin is a protein inhibitor of the wingless signaling pathway of bone formation whose role in osteoimmunology and inflammatory arthritides is still controversial.

## Aim

The aim of the present study was to examine the relation of serum sclerostin as one member of the wingless signal protein inhibitors to arthritic and bony manifestation of psoriasis as a model of autoimmune inflammatory arthritis.

## Settings and design

This was a cross-sectional, prospective study.

## Patients and methods

The study included 30 psoriatic arthritis (PsA) male patients whose mean age was  $43.3 \pm 8.3$  years and had a disease duration of  $3.8 \pm 2.6$  years, and 15 age-matched and sex-matched apparently healthy controls. Serum sclerostin was measured using the enzyme-linked immunosorbent assay. Disease activity was measured using the Disease Activity Index for Psoriatic Arthritis. Ultrasonography of entheses at Leeds enthesitis sites and dual energy X-ray absorptiometry at the lumbar spine were also carried out for all patients.

## Statistical analysis

The independent *t*-test, Pearson's correlation coefficient, and one-way analysis of variance were used for statistical analysis.

## Results

The serum sclerostin level was significantly higher in PsA patients compared with controls, with a mean of 0.64 and 0.37 ng/ml, respectively. Serum sclerostin correlated significantly with Disease Activity Index for Psoriatic Arthritis, ultrasonography inflammatory and damage scores, and dual energy X-ray absorptiometry at the lumbar spine.

## Conclusion

Serum sclerostin could have a significant role in the development of inflammation-associated bone damage in PsA. Further follow-up studies are recommended to confirm the role of serum sclerostin in inflammation and bone damage in PsA patients and the factors that could regulate this autoimmune pathological event.

## Keywords:

Disease Activity Index for Psoriatic Arthritis, dual energy X-ray absorptiometry, Leeds Enthesitis Index, psoriatic arthritis, sclerostin, ultrasonography

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## Introduction

Psoriatic arthritis (PsA) is characterized by focal bone erosions and new bone formation, suggesting an uncoupling of osteoblast–osteoclast homeostasis [1,2].

Sclerostin is an osteocyte-secreted protein encoded by the *SOST* gene [3], an inhibitor of new bone formation [4]. Sclerostin and other wingless (Wnt) pathway inhibitors are implicated in the suppression of bone repair in inflammatory arthritis [5]. However, reduced production of these bone formation inhibitors likely contributes to the excessive bone formation seen early in spondyloarthropathies at entheses [6,7].

This study aimed to examine the relation of serum sclerostin as one member of the Wnt signal protein inhibitors to arthritic and bony manifestation of psoriasis as a model of autoimmune inflammatory arthritis.

## Patients and methods

This cross-sectional study included 30 male patients diagnosed with PsA who fulfilled the diagnostic

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criteria defined according to the Classification Criteria for Psoriatic Arthritis [8]. Patients were randomly recruited from the outpatient clinic of Physical Medicine and Rheumatology at Ain Shams University Hospital. The control group consisted of 15 healthy age-matched and sex-matched volunteers with no history of joint problem and no family history of psoriasis. Both patients and controls had no history suggestive of diabetes, infection, cancer, or other chronic inflammatory disease. Patients on steroids, disease-modifying antirheumatic drugs, or biological therapy within the last 6 months were excluded from the study. The study was conducted in accordance with the World Medical Association Declaration of Helsinki for human patients and was approved by the ethics committee of the Faculty of Medicine Ain Shams University. Furthermore, all participants gave us their written informed consent.

All patients and controls were subjected to the following:

- (1) Full history taking and thorough clinical examination including skin, hair, mucous membrane, and joint examination. BMI was calculated using the Quetelet formula [weight (kg)/height (m<sup>2</sup>)].
- (2) Disease activity was assessed using the Disease Activity Index for Psoriatic Arthritis (DAPSA). The composite score is a simple sum of the scores comprising the sum of tender joint count and swollen joint count, patient global assessment on visual analogue scale (VAS), patient pain on VAS, and C-reactive protein (CRP) level [9]: DAPSA=tender joint count 68+swollen joint count 66+patient global assessment (cm VAS)+patient pain (cm VAS)+CRP (mg/dl). Disease activity states were classified as follows [10]: remission: less than or equal to 4, low disease activity less than or equal to 14, moderate disease activity less than or equal to 28; and high disease activity greater than 28.
- (3) Clinical assessment of enthesitis using the Leed's Enthesitis Index (LEI), which includes an assessment of six sites: bilateral Achilles tendon insertions, medial femoral condyles, and lateral epicondyles of the humerus. Tenderness at each site was quantified, where 0=not tender and 1=tender [11].
- (4) Spinal manifestations were scored according to the Bath Ankylosing Spondylitis Activity Index (BASDAI) [12], which consists of six 10 cm horizontal VASs to measure severity of fatigue, spinal and peripheral joint pain,

localized tenderness, and morning stiffness (both qualitative and quantitative). The final BASDAI score ranges from 0 to 10.

(5) Laboratory examination:

The serum sclerostin level was assessed quantitatively using the enzyme-linked immunosorbent assay by R&D Systems Inc. (USA). Minnesota-based biological products company, USA. Three milliliters of venous blood was collected, centrifuged, and kept at -70°C until analyzed. In this procedure, 20 µl standard/sample/control was added into appropriate wells, followed by 50 µl AB (biotinylated antisclerostin antibody), and then the wells were covered and incubated overnight (18–24 h) at room temperature in the dark. After washing was performed, 200 µl substrate was added and incubated for 30 min at room temperature in the dark. Next, a 50 µl stop solution was added and the absorbance was measured at 450 nm with reference 630 nm.

CRP was measured using nephelometry in patients and controls.

(6) Radiological assessment of the patients:

Ultrasound (US) scans were carried out on a General Electric Logic P-5 using a 10–13 MHz linear probe, at each of the LEI (lateral epicondyles of the humerus, medial condyles of the femur, and Achilles tendon insertions). Gray scale imaging in the longitudinal and transverse planes was used to assess the entheses for the presence of erosions, enthesophytes, bursitis, enthesal thickening, and perienthesal soft-tissue edema. Lesions were scored as present (score 1) or absent (score 0). The assessment of enthesal vascularization was performed using power Doppler. Enteseal vascularity was scored as present (score 1) or absent (score 0).

The US assessments were combined as follows, as an approximation of 'inflammation' and 'damage' at the entheses [13]:

- (1) Inflammation score comprised the four items of vascularization, soft-tissue edema, bursitis, and thickening (score range: 0–4) at each site.
- (2) Damage score comprised the two items of erosion and enthesophyte (score range: 0–2) at each site.

Aggregate scores across all sites were summed up.

In dual energy X-ray absorptiometry, bone mineral density (BMD) was measured for PsA patients only (as part of their routine workup available at time of study). Instrument used for the scans was Lunar DPX-MD+ (GE Medical Systems) at the lumbar spine (L1–L4) in anterior and posterior projections. By dual energy X-ray absorptiometry, results were recorded for each patient as *T* scores (difference in SD from the mean of a healthy young adult) and *Z* scores (difference in SD from the mean of patients same age and sex). Osteoporosis and osteopenia (low bone mass) were defined as *T* scores less than  $-2.5$  and *T* score between  $-1$  and  $-2.5$ , respectively [14].

### Statistical analysis

The clinical, laboratory, and radiological data were written using an IBM-PC with statistical program SPSS, V-19.0 (2010; IBM Corporate, Chicago, USA) to obtain descriptive, analytical, and comparative studies.

### Descriptive statistics

Descriptive statistics were used to detect mean, SD, range, number, and percent.

### Analytical statistics

The independent *t*-test was used for comparison of mean and SD of sclerostin between groups (cases and controls). Pearson's correlation coefficient was used to get the correlation between different quantitative variables. The significance level was set at *P* less than 0.05. One-way analysis of variance was used to compare between different types of BMD in relation to serum sclerostin levels.

## Results

The study included 30 PsA male patients whose ages ranged from 35 to 55 years with a mean of  $43.33 \pm 8.33$  and mean BMI of  $26.87 \pm 2.63$ , and 15 healthy age-matched and sex-matched controls whose ages ranged from 34 to 55 years with a mean of  $42.12 \pm 7.22$  and a

mean BMI of  $25.87 \pm 3.51$ , with an insignificant difference between the two groups regarding age or BMI ( $P < 0.05$ ). Demographic and clinical findings of the patients are presented in Table 1. All of the patients were on nonsteroidal, anti-inflammatory drugs.

Disease activity mean scores, bone density scores, and US radiological scores are presented in Table 2. Most of the patients (57%) had high disease activity scores (DAPSA  $> 28$ ).

The serum sclerostin level was significantly higher in PsA patients, ranging between 0.45 and 1 ng/ml, with a mean of  $0.648 \pm 0.17$ , compared with controls, where the range was from 0.31 to 0.43 ng/ml and the mean was  $0.37 \pm 0.04$  ( $P = 0.000$ ), as seen in Fig. 1. Serum sclerostin levels were significantly higher in patients with bony erosions than in those without erosions ( $P = 0.000$ ) (Table 3 and Fig. 2). CRP was significantly higher in patients compared with controls. Its mean value in patients was  $8.27 \pm 8.97$  mg/dl.

Serum sclerostin showed a positive significant correlation with patients' age, disease activity scores, radiographic findings of inflammation, and damage at the enthesis, as well as BMD at the lumbar spine. A positive though nonsignificant correlation was detected between serum sclerostin and LEI and CRP.

US inflammation and damage scores both showed significantly positive correlation with disease activity scores, and a negative significant correlation with BMD. US damage score correlated positively with LEI. Although nonsignificant, a positive correlation was detected between US inflammation score and LEI. Some of our recorded data are shown in Fig. 3. Erosion in medial femoral condyle, edema, and active power Doppler signs are shown in Fig. 4, and calcifications in Fig. 5.

Regarding bone density at the lumbar spine, 43.3% of the patients had normal bone density, 33.3% had

**Table 1** Demographic and clinical findings of psoriatic arthritis patients ( $n=30$ )

	Mean	SD
Age	43.33	8.339
BMI	26.87	1.776
Duration of psoriasis	13.03	8.640
Duration of psoriatic arthritis	3.80	2.677
Dactylitis	2.20	3.199
Enthesitis	2.93	2.100
TJC	10.93	6.357
SJC	4.43	4.812

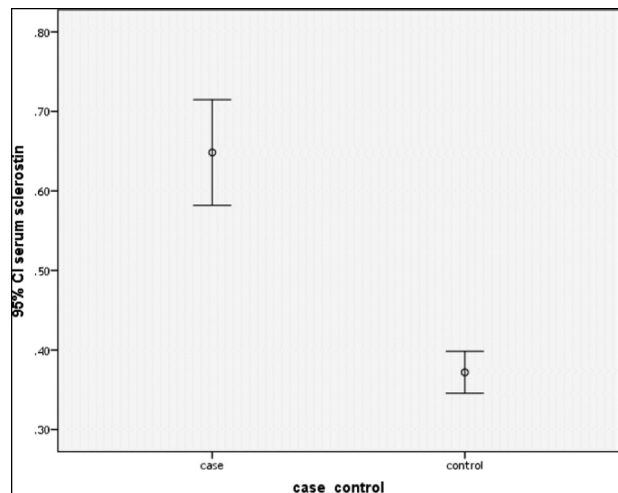
SJC, swollen joint count; TJC, tender joint count.

**Table 2** Disease activity and radiological scores of psoriatic arthritis patients ( $n=30$ )

	Mean	SD
DAPSA	56.20	17.572
BASDAI	5.203	2.1440
DEXA Lumbar	1.0334	0.15526
<i>T</i> score	$-1.5733$	1.27629
Inflammatory US index	9.20	2.384
Damage US index	3.37	1.629

BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; DAPSA, Disease Activity Index for Psoriatic Arthritis; DEXA, dual energy X-ray absorptiometry; US, ultrasound.

Figure 1



Error bar graph showing significant difference in sclerostin levels between cases and controls.

**Table 3 Serum sclerostin levels in psoriatic arthritis patients and controls**

	Patients (30) (mean±SD)	Controls (15) (mean±SD)	T	P
Sclerostin (ng/ml)	0.648±0.1779	0.372±0.0475	7.96	0.000*

\*Denotes highly significant.

**Table 4 Comparison between serum sclerostin levels in patients with and without erosions**

	Erosion	N	Mean	SD	T	P
Serum sclerostin	No erosion	13	0.5000	0.04564	-6.574	0.000*
	Erosion	17	0.7618	0.15565		

\*Denotes highly significant.

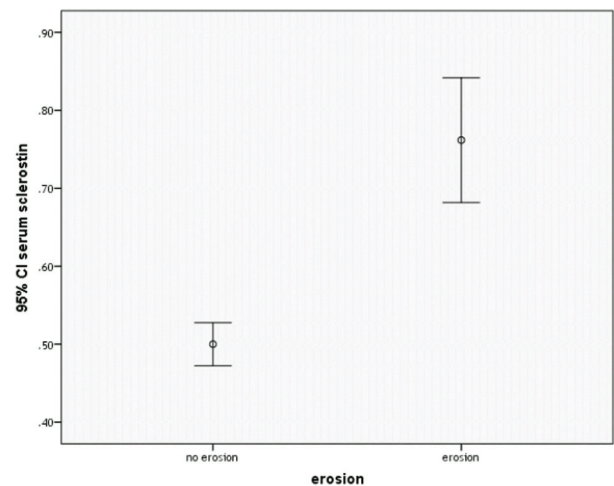
osteopenia, and 23.3% were osteoporotic. A significant difference in the serum sclerostin level was detected between patients with different grades of osteoporosis using analysis of variance analysis, as seen in Table 4. A post-hoc analysis revealed significant difference in the serum sclerostin level between patients with normal bone mass and in those with osteoporosis and osteopenia; similarly a significant difference was observed between osteoporotic and osteopenia patients as regards serum sclerostin ( $P < 0.001$ ) (Tables 5 and 6).

## Discussion

The role of serum sclerostin in PsA is still to be understood. PsA involves the dual mechanism of bone resorption and new bone formation.

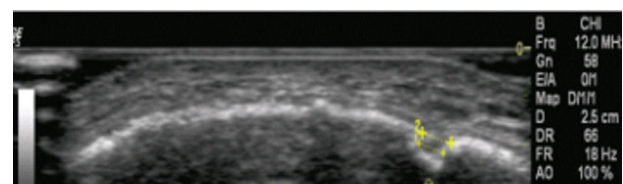
In this study, the serum sclerostin level was significantly higher in PsA male patients compared with normal

Figure 2



Error bar graph showing significant difference in sclerostin levels in patients with and without erosions.

Figure 3



Ultrasonographic transverse scan of the medial condyle of the femur showing step-down depression denoting erosion measuring 0.19 cm.

Figure 4

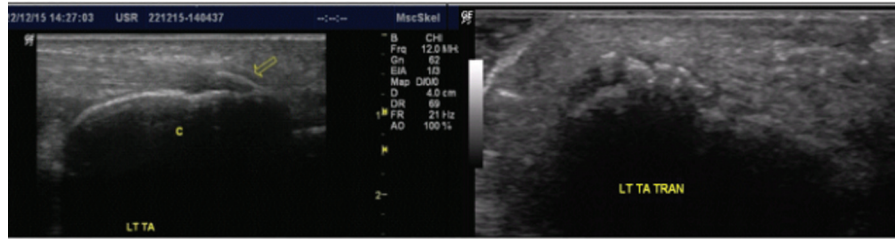


Ultrasonographic longitudinal scan of the tendoachillis showing hypoechoic area of edema and power Doppler signal grade I at the site of insertion of tendon at the calcaneus.

healthy age, sex, and BMI-matched controls. The findings of previous studies on rheumatoid arthritis have been controversial, as some found that the serum sclerostin level was much higher in patients compared with controls [15,16] and others found no significant difference in the levels between patients and controls, but this could be explained by the fact that most of the patients in that study were under medical control using methotrexate and were in a state of remission [17]. Previous studies on spondyloarthropathy patients revealed that the levels were significantly lower in patients compared with controls. However, PsA has



Figure 5



Ultrasonographic longitudinal (a) and transverse scan (b) of the tendoachillis showing hyperechoic calcification at the calcaneus with bone irregularity (site of insertion of Achilles tendon).

**Table 5 Comparison between serum sclerostin levels in psoriatic arthritis patients with different grades of osteoporosis**

	Serum sclerostin (ng/ml)		Minimum	Maximum	F	P
	Mean	SD				
Normal (n=13)	0.563	0.1025	0.4	0.7	15.988	0.000*
Osteoporosis (n=7)	0.804	0.1658	0.6	0.10		
Osteopenia (n=10)	0.508	0.204	0.5	0.6		

\*Denotes highly significant.

**Table 6 Correlation between both serum sclerostin levels and ultrasonographic findings at the enthesis with each of demographic, clinical findings, disease activity indices, radiological, and laboratory findings in psoriatic arthritis patients**

	Age	DD	LEI	BASDAI	DAPSA	BMD	US inflam	US dmg	CRP
US inflam	NS	NS	NS	0.712**	0.863**	-0.539*	1	0.682*	NS
US dmg	NS	NS	0.229**	0.564**	0.497*	-0.705*	682*	1	NS
Sclerostin	0.456*	NS	NS	0.798**	0.623**	-0.649**	0.814**	0.758**	NS

BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BMD, bone mineral density; CRP, C-reactive protein; DAPSA, Disease Activity Index for Psoriatic Arthritis; DD, psoriatic arthritis duration; dmg, damage score; inflam, inflammation score; LEI, Leed's Enthesitis Index; US, ultrasound. \*Significant at  $P < 0.05$ . \*\*Significant at  $P < 0.001$ .

different patterns of presentation, and owing to the fact that most of our patients presented with peripheral arthritis rather than axial, spondyloarthropathy could explain the fact that serum sclerostin was higher in patients compared with controls.

A previous study has shown that tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) causes upregulation of the Wnt inhibitors, Dickkopf-related proteins (Dkk-1), and sclerostin, and thus may suppress osteoblast-mediated bone formation by the inhibition of the Wnt- $\beta$ -catenin pathway [18]. Both conventional as well as biological disease-modifying antirheumatic drugs have been shown to decrease osteoclastic activity and have a positive effect on BMD in rheumatoid arthritis patients [19].

In a recent work by Tahrani *et al.* [20], serum sclerostin levels were found to be significantly lower in PsA patients compared with controls. However, in their study most of the patients were controlled on medications including corticosteroids, methotrexate, and anti-TNF, and their mean disease activity scores were much lower than that of our patients. Wehmeyer *et al.* [21] in an animal model of induced arthritis found that sclerostin blocks TNF- $\alpha$ -induced p38 and nuclear

factor- $\kappa$ B activation and have an unrealized protective role in TNF-mediated chronic inflammation. We hypothesize that increased serum sclerostin in our patients could be a protective compensatory mechanism to the increased disease activity.

In the present study, serum sclerostin showed a positive significant correlation with age in patients and controls. A previous study by Amrein *et al.* [22] elaborated that in healthy adults, sclerostin serum levels correlated positively with age. However, there was no significant difference as regards age between patients and controls in our study. As regards disease activity in this study, a significant positive correlation was found between the serum sclerostin level in patients and each of BASDAI and DAPSA disease activity scores, as well as US findings of inflammation and damage at the enthesis. A positive, though nonsignificant, relation was detected between serum sclerostin and LEI and CRP. Previously, in their respective studies on Rheumatoid Arthritis (RA) patients, Ibrahim *et al.* [15 and El-Bakry *et al.* [16], serum sclerostin was shown to have a significant positive correlation with both disease activity scores and radiographic inflammation and erosion scores using magnetic resonance imaging.

In our study, US inflammation scores significantly positively correlated with clinical disease activity scores. This is in agreement with the findings of a previous study on PsA patients that revealed that US findings of inflammation using B-mode US and power Doppler better correlated with the DAPSA composite score of disease activity [23].

Serum sclerostin showed a negative significant correlation with BMD at the lumbar spine. A significant difference in the serum sclerostin level was detected between patients with different grades of BMD. Sclerostin levels were higher in osteoporotic and osteopenic patients compared with patients with normal BMD. In a study on RA patients, a significant correlation between serum sclerostin levels and BMD in these patients was found [24,25].

Antisclerostin antibodies showed promising results to stimulate bone formation in patients with osteoporosis [26]. However their role in inflammation and joint damage is still controversial. In the different form of chronic arthritis, lack of Wnt signaling could impair repair of erosions, whereas excessive or dysregulated pathway activation can lead to joint or spine ankylosis [27]. Although another study, conducted by Wehmeyer *et al* [21], reported that sclerostin inhibition promoted TNF-dependent inflammatory joint destruction, a study in the murine model of rheumatoid arthritis revealed that sclerostin blockade prevented or reversed the decrease in axial and appendicular bone mass but did not affect systemic inflammation and was unable to prevent or repair local focal erosion [28].

### Conclusion and recommendations

The significantly higher serum sclerostin levels in PsA patients, especially those with bone erosions, compared with controls; significant positive correlation with disease activity scores, US inflammatory scores, and damage scores; and negative correlation with BMD highlight the fact that sclerostin plays an important role in the pathogenesis of PsA and its associated bone damage, either systemic or localized. We can hypothesize that the increased serum sclerostin is a compensatory mechanism to inflammatory process. The use of antisclerostin or other Wnt signaling inhibitors in PsA is still to be investigated because of the risk for increased new bone formation.

Further follow-up studies for the effect of treatment on change in serum sclerostin and associated US findings and BMD findings are recommended.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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