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Serum sclerostin as a biomarker of disease activity in ankylosing spondylitis in correlation with radiographic imaging

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Abstract

Background The wingless signaling pathway of bone development is inhibited by sclerostin, which may contribute to the etiology of ankylosing spondylitis.

Aim The study aimed to evaluate serum sclerostin levels in ankylosing spondylitis patients and investigate how it correlated with radiographic damage using the Spondylo-arthritis Research Consortium of Canada index (SPARCC), disease activity, and functional impairment.

Results This cross-sectional case–control study revealed a significantly lower mean serum sclerostin (11.28 ng/ml) in AS patients compared with controls (101.25 ng/ml). Serum sclerostin levels showed a significant negative correlation with each of Bath Ankylosing Spondylitis Metrology Index (BASMI) ($p=0.043$), sacroiliac joints SPARCC, spine SPARCC, and overall SPARCC scores ($p=0.012$, $p=0.036$, and $p=0.007$). The detection of AS, serum sclerostin levels ≤ 20 ng/ml showed 100% sensitivity and specificity.

Conclusion Serum sclerostin had good discriminating power between ankylosing spondylitis cases and healthy control individuals and was correlated with subclinical activity status on magnetic resonance imaging.

Keywords Ankylosing spondylitis, Disease activity, Sclerostin, MRI, SPARCC score

Background

Axial and peripheral entheseal inflammation associated with new bone formation are the hallmarks of ankylosing spondylitis (AS) [1]. The growth of syndesmophytes results in spinal fusion and functional disability [2]. It has recently been studied how the wingless signaling pathway (Wnt/-catenin pathway) and its inhibitors contribute to the pathophysiology of AS. The canonical Wnt pathway's initiation, results in the transcription of genes essential for osteoblast growth and the creation of new bone. Therefore, the decreased Wnt inhibitors or their impaired function might be involved in AS pathogenesis. Sclerostin is a secreted glycoprotein expressed by the SOST gene "the gene that provides instructions for making the protein sclerostin" [3]. Osteocytes and some chondrocytes predominantly generate it. Since it inhibits the Wnt signaling pathway, sclerostin has been shown to have anti-anabolic effects on the growth of new bone [4, 5].

The study aimed to assess the serum sclerostin level in patients with AS and look for any relationships with disease activity, radiographic damage, and functional impairment.

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Patients and methods

This cross-sectional case–control study included twenty AS male patients aged 25 to 45 who met the Assessment of SpondyloArthritis International Society (ASAS) criteria for axial spondyloarthritis [6]. Twenty age-matched males served as controls. All participants provided written informed consent. The ethics committee approved the study.

Every participant underwent the following:

1) Full medical history includes disease duration, degree of back pain using VAS, morning stiffness duration, and extraarticular manifestations (e.g., uveitis, and psoriasis).
2) Clinical examination with special concern about skin, nails, hair, peripheral, and axial joint examination. BASMI was measured for spinal mobility [7].
3) Evaluation of AS disease activity by Bath AS disease activity (BASDAI) [8] and Ankylosing Spondylitis Disease Activity Score (ASDAS) [9], functional status by Bath ankylosing spondylitis functional index (BASFI) [10].
4) Comprehensive blood counts (CBC), erythrocyte sedimentation rates (ESR), C-reactive protein (CRP), and HLA-B27 were all measured in a lab setting.
5) A modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) was used to perform and evaluate radiographs of the spine and pelvis [11]. The involvement of the sacroiliac joints was assessed using the New York criteria [12].
6) Both sacroiliac joints (SIJs) underwent magnetic resonance imaging (MRI), which included coronal oblique T1-weighted and short tau inversion recovery (STIR) images of the SIJs, as well as assessments of the SpondyloArthritis Research Consortium of Canada index (SPARCC) and six consecutive coronal oblique layers [13].
7) Quantitative Assessment of serum sclerostin level was performed using a Human Sclerostin enzyme immunoassay (ELISA) Kit (Bioassay Technology Laboratory, Zhejiang, China). Blood from the patient was drawn during the visit in three milliliters, centrifuged, and stored at -70 °C for analysis. The kit was completed for both patients and controls according to the manufacturer's instructions that were included in the kit.

Statistical analysis

The statistical software for social sciences, version 23.0 (SPSS Inc., Chicago, Illinois, USA), was used to analyze the recorded data. Mean ± standard deviation (SD) and ranges were used to show the quantitative data. Numbers and percentages were also used to represent qualitative characteristics. When comparing two means, the independent t-test of significance was employed.

The Chi-square test was used to compare groups based on qualitative data. The degree of correlation between two variables was evaluated using Pearson's correlation coefficient (r) test. Utilizing the Receiver Operating Characteristic (ROC) curve analysis, the overall predictivity of the parameter was determined, along with the optimal cut-off value. *P*-values less than 0.05 were considered significant, and *P*-values greater than 0.05 were insignificant.

Results

Twenty male AS patients, aged 25 to 45, with a mean age of 37.80 ± 7.02 and a mean disease duration of 6.4 ± 2.3 years, and twenty healthy age and sex-matched controls, aged 25 to 45, with a mean age of 37.75 ± 7.05, were included in this case–control study. All patients were on biological therapy. According to ASDAS, most patients had high disease activity, with a mean ± SD of 3.01 ± 0.81. Comparing ESR and CRP levels of the investigated cases to the control group, the AS patients showed substantial statistical differences (Table 1).

The mSASSS score of the spines in AS patients ranged from 2 to 19, With a mean ± SD of 8.40 ± 5.10.

Table 1 The demographic, clinical, laboratory, and radiological findings of AS patients (*n* = 20)

Data	AS male patients (*n* = 20)
Age (years), Mean ± SD/ Range	37.80 ± 7.02 (25–45)
Disease duration (years), Mean ± SD/ Range	6.4 ± 2.3 (3–11)
HLA-B27 positivity, n (%)	20 (100.0%)
CRP, mg/dl, Mean ± SD/ Range	38.55 ± 18.66 (17–76)
ESR mm/hr, Mean ± SD/ Range	30.35 ± 5.53 (21–39)
ASDAS, Mean ± SD/ Range	3.01 ± 0.81 (1.9–4.8)
BASDI, Mean ± SD/ Range	4.13 ± 0.73 (2.4–5.1)
BASMI, Mean ± SD/ Range	3.76 ± 0.41 (2.9–4.4)
BASFI, Mean ± SD/ Range	5.64 ± 0.79 (4.2–6.7)
Sacroiliitis, I grade, n (%)	5 (25.0%)
Sacroiliitis II grade, n (%)	9 (45.0%)
Sacroiliitis III grade, n (%)	6 (30.0%)
mSASSS, Mean ± SD/ Range	8.40 ± 5.10 (2–19)
SIJs SPARCC score, Mean ± SD	17.60 ± 12.10
Spine SPARCC score, Mean ± SD	16.74 ± 10.80
Total SPARCC score, Mean ± SD	34.34 ± 22.90

CRP C-reactive protein, *ESR* erythrocyte sedimentation rate, *ASDAS* Ankylosing Spondylitis Disease Activity Score, *BASMI* Bath Ankylosing Spondylitis Metrology Index, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *BASFI* Bath Ankylosing Spondylitis Functional Index, *mSASSS* Stoke Ankylosing Spondylitis Spinal Score, *SPARCC* SpondyloArthritis Research Consortium of Canada index

Five of the patients (25.0%) had Grade 1 sacroiliitis, 9 patients (45.0%) had Grade 2, and 6 patients (30.0%) had Grade 3 and patients were classified into mild, moderate, and severe, respectively. The mean ± SD of the SIJs SPARCC score was 17.60 ± 12.10; the spine SPARCC score was 16.74 ± 10.80; and the total SPARCC score was 34.34 ± 22.90 (Figs. 1 and 2).

Table 2 indicates a significant decrease in the serum concentrations of sclerostin in AS patients. Serum Sclerostin AS patients' levels are represented by the ROC curve in Fig. 3. Higher sensitivity (100%) and specificity (100%) were observed for serum levels ≤ 20 ng/ml.

Table 3 summarizes the relationships between serum sclerostin levels and clinical, laboratory, and radiographic information AS patients. The BASMI score ($p = 0.043$), ESR, and CRP ($p < 0.001$) all exhibited a statistically significant negative correlation with serum sclerostin. No statistically significant correlation was found between serum sclerostin levels and each of BASDAI, BASFI, or ASDAS ($p > 0.05$). The level of serum sclerostin was found to be negatively correlated ($p < 0.05$) with the SIJ SPARCC score, spine SPARCC score, and total SPARCC score (Fig. 4). Despite this, there was no statistically significant link between the sacroiliac joint grading and spine radiographs, as indicated by Table 3. A substantially significant positive correlation was found between the mSASSS and BASMI ($r = 0.409$, $p = 0.030$).

Discussion

Understanding the pathophysiology of AS is essential to prevent bone formation, which is a major contributor to disability and a lower quality of life (QoL), particularly in cases where the disease is more active, the functional handicap is greater, the peripheral joints are more involved, and the spinal mobility is reduced [14].

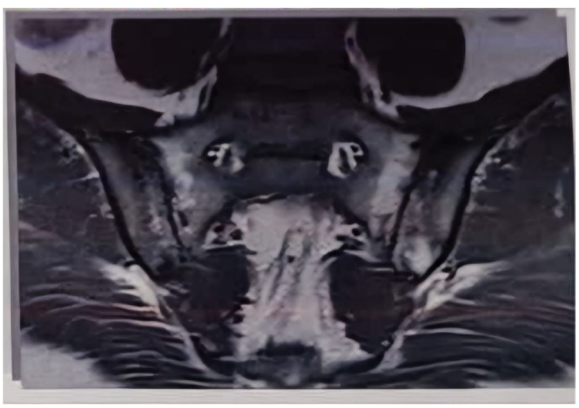

Fig. 1 T2 MRI of SIJs (coronal view) of a 34-year-old male AS patient with 3 years of disease duration, positive HLA-B27 showed bilateral active sacroiliitis evident by bone marrow edema (blue arrows) and erosions (yellow arrow) "SPARCC score 19"

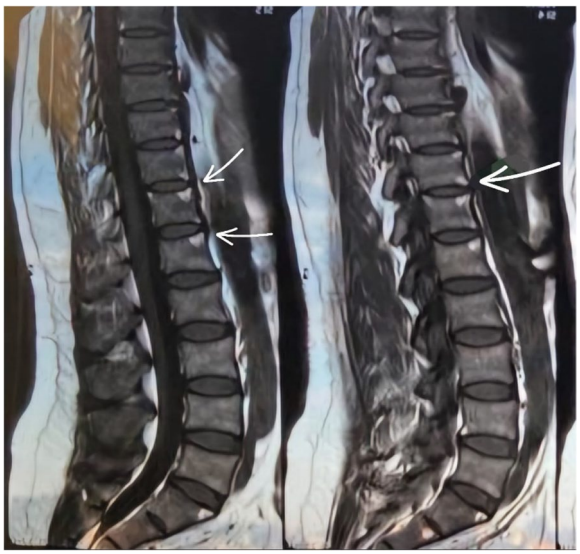

Fig. 2 T2 MRI of the spine (sagittal view) of a 34-year-old male AS patient with 5 years of disease duration, positive HLA-B27 showed spondylitis evident by bone marrow edema shiny corners (arrows) "SPARCC score 23"

We found the serum sclerostin level was considerably lower in male AS patients. The results of earlier research [15–17] are consistent with this observation.

In an earlier investigation, Appel et al. discovered that their AS patients had low serum and local bone tissue samples of sclerostin expression levels. This supports the theory of facilitated osteoblastic cell activation and differentiation by decreased Wnt inhibitor expression [2].

However, compared to the control group, Wakhulu et al. demonstrated that the AS patient group had a noticeably greater amount of serum sclerostin [18]. This could be explained by the fact that they did not include any patients getting biological treatment, which contrasted sharply with our results.

Moreover, in this work, serum sclerostin showed good diagnostic performance and was able to differentiate AS patients from controls with high sensitivity (100%) and specificity (100%) at a cut-off value ≤ 20 ng/ml.

Table 2 Serum sclerostin levels in AS patients and controls

Serum sclerostin level (ng/ml)	AS Group ($n = 20$)	Control ($n = 20$)	Test value	*P*-value
Mean ± SD	11.28 ± 3.81	101.25 ± 42.17	-9.502	< 0.001**
Range	7.5–20	50–210		

Using: t-Independent Sample t-test for Mean ± SD

** *p*-value < 0.001 is significant

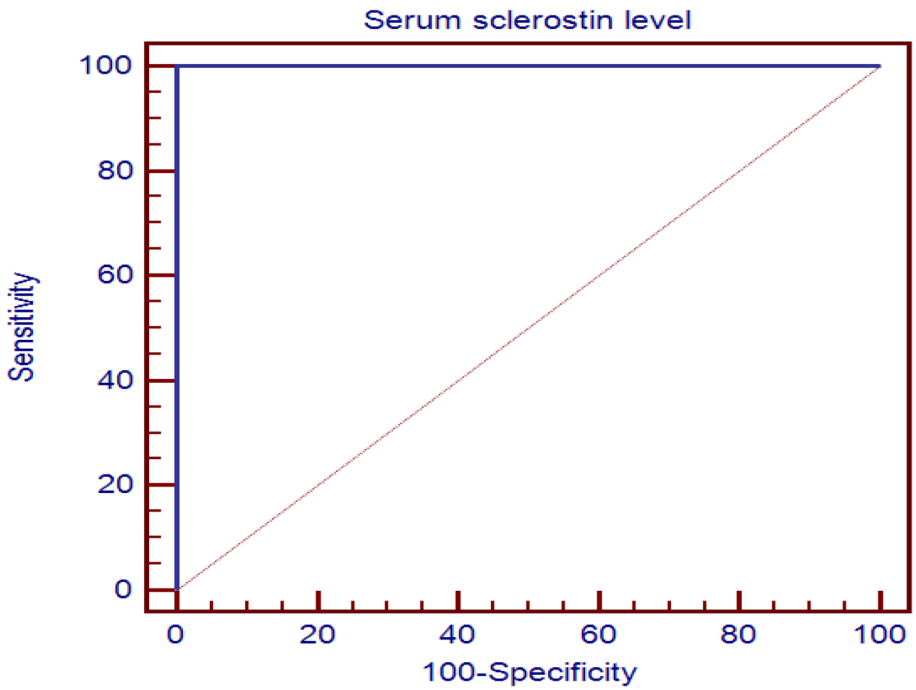

Fig. 3 Receiver operating characteristic (ROC) curve for serum levels of sclerostin in AS patients ($N=20$) and in healthy controls ($n=20$). Area under the curve (AUC): 1.000; 95%confidence interval: 0.912–1.00

Table 3 Correlation between serum sclerostin levels and clinical, laboratory, and radiological parameters in AS patients

Parameters	Serum sclerostin level	
	r-value	*p*-value
ESR	-0.805	< 0.001**
CRP	-0.628	< 0.001**
BASMI score	-0.406	0.043*
BASDAI	0.130	0.586
BASFI	-0.082	0.732
ASDAS	-0.298	0.201
mSASSS	0.116	0.626
Radiographs of sacroiliac joint grade	-0.125	0.598
SIJs SPARCC score	-0.503	0.012*
Spine SPARCC score	-0.432	0.036*
Total SPARCC score	-0.680	0.007*

r-Pearson Correlation Coefficient, *p*-value > 0.05 is insignificant

CRP C-reactive protein, *ESR* erythrocyte sedimentation rate, *ASDAS* Ankylosing Spondylitis Disease Activity Score, *BASMI* Bath Ankylosing Spondylitis Metrology Index, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *BASFI* Bath Ankylosing Spondylitis Functional Index, *mSASSS* Stoke Ankylosing Spondylitis Spinal Score, *SPARCC* SpondyloArthritis Research Consortium of Canada index

**p*-value < 0.05 is significant

***p*-value < 0.001 is highly significant

Sclerostin levels were not shown to be correlated with either the BASDI or the ASDAS. Other research [2, 16, 19] reported similar outcomes. Saad et al. speculate that the low sample size and the possibility of additional cytokines or cellular mechanisms contributing to the downregulation of sclerostin expression could explain this finding [20]. However, we did not discover a meaningful association between serum sclerostin levels and the mSASSS. Previous research [15, 21] found results like these. Between the mSASSS and BASMI, we discovered a statistically significant positive correlation.

Inflammation and the production of new bone are correlated, according to Perotta et al. [15]. However, neither the existence of inflammation, the disease duration, nor the degree of disease activity affected sclerostin levels. Its role in the pathophysiology of AS is supported by the low serum levels of sclerostin in AS patients compared to controls.

Additionally, we found a statistically significant inverse relationship between the total SPARCC score, the spine SPARCC score, and the serum sclerostin' level in SIJs. In line with Lau et al.'s findings [22], who discovered that neither the disease activity scores nor SPARCC showed a link. The lack of correlation may be attributed

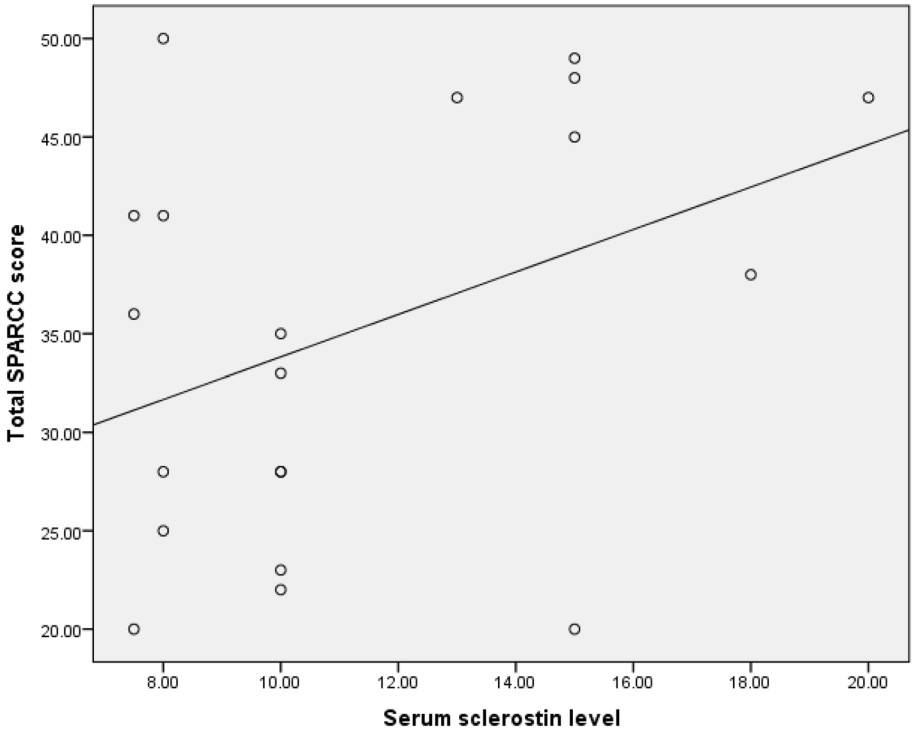

Fig. 4 The Scatter plot between serum sclerostin level and total SPARCC score

to the subjective nature of certain clinical disease activity scores, which rely on the experiences of individual patients. More research on a larger scale and with subgroup analysis could be required to assess this aspect.

Zhang et al. [23] showed a statistically significant correlation between clinical activity indices with SPARCC, which disagreed with our results. The fact that their sample size was greater (55 patients) might help to explain this.

The findings of our investigation point to a potential function for sclerostin in the diagnosis of AS patients. More research with large patient numbers is necessary to validate the role of sclerostin in disease activity and the condition's advancement.

Limitation of the study

1. This cross-sectional case–control study prevents the establishment of causal relationships; so longitudinal studies and follow-up are necessary to confirm the correlation of Sclerostin to disease activity and disease progression.
2. A small number of patient groups in the study; so, a wide scale of patients is needed to confirm the sensitivity and specificity of Sclerostin.

Conclusion

Serum sclerostin linked with MRI findings of disease activity, which may indicate subclinical activity status, and demonstrated good discriminating ability between cases of ankylosing spondylitis and healthy control subjects.

Abbreviations

AS	Ankylosing spondylitis
ASAS	Assessment of spondyloArthritis international society
ASDAS	Ankylosing spondylitis disease activity score
BASDAI	Bath AS disease activity
BASMI	Bath metrology index
BASFI	Bath ankylosing spondylitis functional index.
mSASSS	Modified stoke ankylosing spondylitis spinal score
SPARCC	SpondyloArthritis research consortium of Canada index

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Authors' contributions

Nouran Medhat examined, analyzed, and interpreted the patient data regarding the disease. Marwa Ahmed was a major contributor to 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 upon reasonable request.

Declarations

Ethics approval and consent to participate
All participants provided written informed consent. The study was conducted by 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 No. FMASU: MS 239/2022.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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