Bone mineral density and serum sclerostin levels in early ankylosing spondylitis: their possible correlation with a panel of disease activity and structural change parameters
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Objective
The aim of this study was to investigate decreased bone mineral density (BMD) and serum sclerostin levels in early ankylosing spondylitis (AS) and to determine their possible correlation with a panel of disease activity parameters, functional impairment, bone turnover markers and syndesmophyte formation.

Methods
A total of 37 male patients having early AS with a disease duration of less than 10 years were included into the study and divided into two groups (group I, <5 years and group II, 5–10 years). The study also included 30 apparently healthy controls. The assessment included demographic data, clinical examination and measurement of the C-reactive protein (CRP)-based Ankylosing Spondylitis Disease Activity Score (ASDAS), the Bath Ankylosing Spondylitis Functional Index (BASFI), the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS), BMD measurement of lumbar spine and hip using dual-energy X-ray absorptiometry and determination of erythrocyte sedimentation rate (ESR), CRP levels, creatinine levels, bone alkaline phosphatase (BALP) levels, serum levels of C-telopeptides of type I collagen (sCTX) and sclerostin levels.

Results
Osteopaenia and osteoporosis of the lumbar spine were observed in 47 and 23.53% and in 35 and 15% of patients in group I and II, respectively. In the proximal femur, osteopaenia and osteoporosis were detected in 35.3 and 17.65% and in 45 and 25% of individuals in group I and II, respectively. ESR, CRP and sCTX levels were significantly higher in patients than in controls, with an insignificant difference between the patient groups. BALP levels showed an insignificant difference between the three groups. Serum sclerostin levels were significantly lower in AS patients compared with controls and in group II patients compared with those of group I. A low BMD correlated negatively with parameters of disease activity (ESR, CRP and ASDAS), BASFI scores and sCTX levels. No correlation was demonstrated between low BMDs and mSASSS and between BALP and sclerostin levels. Sclerostin showed a negative correlation with disease activity parameters (ESR, CRP and ASDAS), BASFI scores, sCTX levels, and mSASSS.

Conclusion
A low BMD is common in early AS patients; the role of inflammation seems to be pivotal in its pathogenesis. The monitoring of bone turnover markers and disease activity indices may help to predict patients at risk. Sclerostin expression is impaired in early disease and was linked to disease activity, bone turnover markers and increased structural damage, emphasizing the role of sclerostin in the pathogenesis of AS.

Keywords:
ankylosing spondylitis, bone mineral density, bone turnover markers, sclerostin

Introduction
Ankylosing spondylitis (AS) is a chronic, disabling rheumatic disease characterized by inflammatory back pain, restricted spinal mobility, frequent peripheral arthritis, enthesitis and acute anterior uveitis [1]. Inflammatory enthesopathy progressing to ossification and ankylosis is the pathological basis for the disease [2].

In AS, two enhanced but opposite bone remodelling processes take place in close vicinity to the spine; these are pathological new bone formation in the cortical...
zone of the vertebrae, the zygapophyseal joints and the ligamentous apparatus and excessive loss of trabecular bone in the centre of the vertebral body leading to osteoporosis (OP) [3].

The cortical bone contains osteocytes located in lacunae that are connected by channels that physiologically produce sclerostin, a potent suppressor of bone formation [4]. Sclerostin selectively inhibits Wnt/β-catenin, suppressing the activity of osteoblasts and viability of osteoblasts and osteocytes [5,6]. A role of Wnt proteins has been implicated in the formation of bony spurs, such as syndesmophytes in AS [7].

OP in terms of decreased bone mineral density (BMD) is a common complication in AS patients that has also been shown to present in mild AS patients and during early disease [8]. The prevalence ranges from 19 to 62% [9]. Few studies have shed light on the relation between inflammation and low BMDs in AS patients, as evidenced by elevated erythrocyte sedimentation rate (ESR) or CRP levels [10,11]. Other reports suggest that inflammation may play a major role in the occurrence of OP in AS [11]. The decrease in BMDs can be reported both in the hip and spine and depends on disease duration and the presence of syndesmophytes in the spine [12].

In advanced AS, it can be difficult to interpret lumbar spine BMDs measured using dual-energy X-ray absorptiometry in the anteroposterior projection. The new bone formation characteristic of AS causes an overestimation of the total BMD, and the values can be normal or high, even when OP is present [3].

Aim of the study
The knowledge of the prevalence of decreased BMDs and serum sclerostin levels in early AS is limited. Therefore, this study was carried out to investigate the decrease in these values in early AS (≤ 10 years) and to determine their possible correlations with a panel of disease activity parameters, functional impairment, bone turnover markers and syndesmophyte formation.

Patients and methods
A total of 37 male AS patients fulfilling the ASAS classification criteria for axial spondyloarthropathies [13], in addition to 30 apparently healthy individuals serving as controls, were enrolled into the present study. A disease duration, defined as the time elapsed between first symptoms and enrolment, of less than 10 years was the inclusion criterion for our study. Patients were divided into two groups (group I having a disease duration of < 5 years and group II with a duration of 5–10 years).

Patients with inflammatory bowel disease or psoriasis, history of thyroid or parathyroid disorders or chronic renal or liver diseases, those on anticonvulsants, systemic high-dose corticosteroids and bisphosphonates or those having excessive alcohol intake were excluded from the study. All patients were receiving NSAIDs and/or sulfasalazine but none were on anti-tumor necrosis factor (TNF)-α therapy. The assessment included demographic data (age, height, weight and BMI in kg/m²), clinical examination and measurement of disease activity and functional ability using the CRP-based Ankylosing Spondylitis Disease Activity Score (ASDAS) [14]; Patients were classified as having inactive disease if the score was less than 1.3, moderate disease activity if it was 1.3–2.1, high disease activity if it was 2.1–3.5 or very high disease activity if the score was 3.1. The Bath Ankylosing Spondylitis Functional Index (BASFI) [15] includes eight items of daily activities and two items that assess the patient’s ability to cope with everyday life. Each item is answered on a 10-cm horizontal numerical rating scale. The final score (ranging from 0 to 100) is the average of the scores on the 10 items. Higher scores indicate more severe impairment.

Radiological scoring
Cervical and lumbar lateral radiographs were scored using a detailed scoring method assessing the anterior corners of the vertebrae by the same clinician. The modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) [16] scores every corner of the anterior site of the lumbar and cervical vertebrae on a scale of 0–3, in which 0 indicates no abnormality; 1 indicates erosion, sclerosis or squaring; 2 indicates a syndesmophyte; and 3 indicates a bridging syndesmophyte. The total score is the sum of both scores and ranges from 0 to 72 (0–36 for the cervical spine and 0–36 for the lumbar spine). The cervical spine is scored from the lower border of the second cervical vertebra to the upper border of the first thoracic vertebra, and the lumbar spine is scored from the lower border of the 12th thoracic vertebra to the upper border of the sacrum.

Bone density measurement
BMD measurements of lumbar spine (anteroposterior projection at L1–L4) and hip (total proximal femur) were measured using dual-energy X-ray absorptiometry (Hologic QDR Discovery (UMCG) or Hologic QDR Delphi (MCL); Hologic, Waltham, Massachusetts, USA), the results were expressed as g/cm². According to the WHO classification, a normal bone density was defined as a T score ≥ –1.0, osteopaenia as –2.5 < T score < –1.0, and osteoporosis T score ≤ –2.5 [17].

Biochemical analysis
Biochemical assays were performed on fasting morning blood samples obtained concurrently with assessment of clinical parameters. Blood analysis was performed either within the 2 h after drawing of blood or with thawed sera that had been stored at –70°C before analysis.

Sera were submitted for biochemical analysis, including determination of ESR and levels of CRP, creatinine (to ensure normal renal function), bone alkaline phosphatase (BALP), serum C-telopeptides of type I collagen (sCTX) and sclerostin.

Serum BALP levels were determined using enzyme immunoassays (EIA; Metra Biosystems, Mountain View, California, USA), according to the manufacturer’s protocol. The bone resorption marker sCTX was measured using electrochemiluminescence immunoassays (ECLIA,
Elecsys 2010, Roche, Mannheim, Germany) (IE-CV 10.8%). Serum levels of sclerostin were quantified using commercial sandwich ELISA assays (cat. no.: BI-20492; BiomedicaGruppe, Vienna, Austria). The detection limit of sclerostin on ELISA was 3.2 pmol/l.

Statistical analysis
All data were analysed using the SPSS software (version 11; SPSS Inc., Chicago, Illinois, USA). The baseline characteristics are presented as mean ± SD for continuous variables and as frequency and percentage for discrete ones. Comparisons between the groups were made using analysis of variance. Correlations between variables were examined using Pearson’s correlation coefficient. A P value of less than 0.05 was considered statistically significant.

Results
In the present study, 17 (46%) AS patients had a disease duration of less than 5 years, whereas 20 (54%) had a duration of 5–10 years. The mean age was 30.6 ± 10.5 years for patients in group I, 35.6 ± 8.8 years for those in group II and 33.7 ± 10.8 years for controls, with an insignificant difference among the three groups. Both patients and healthy controls had comparable BMI (22.5 ± 5, 21.1 ± 4.2 and 23.6 ± 2.2 kg/m², respectively).

The median disease duration in group I was 3.2 ± 2.3 years, whereas that in group II was 7.6 ± 2.3 years. Axial involvement was observed in 19 patients (51.35%), whereas axial and peripheral involvement mainly affecting the hip and knee joints was observed in 18 (48.65%) patients.

The patients showed moderate-to-high disease activity in both groups, with an insignificant difference among them on using ASDAS. In contrast, the BASFI scores showed a significant increase of the score in group II compared with group I. mSASSS were significantly higher in group II compared with group I (23.35 ± 19.0 and 16.5 ± 14.9, respectively).

Osteopaenia and OP of the lumbar spine were observed in group I in 47 and 23.53% of patients, respectively and in the femoral neck in 35.3 and 17.65% of patients, respectively. Meanwhile, in group II, osteopaenia and OP were observed in the lumbar spine in 35 and 15% of patients, respectively and in the femoral neck in 45 and 25% of patients, respectively. Hip BMDs were significantly lower in group II compared with group I, and the lumbar spine showed an insignificant increase in BMD values, whereas both groups had significantly lower BMD values compared with controls.

The ESR and levels of CRP and sCTX were significantly higher in patients than in controls, with an insignificant difference among the two patient groups. In contrast, the BALP levels showed an insignificant difference among the three groups. Serum sclerostin levels were significantly lower in AS patients compared with controls and in group II compared with group I (Table 1).

No correlation was found between the clinical and laboratory parameters and BMD and the patient’s age or disease duration.

A low BMD correlated negatively with the parameters of disease activity (ESR, CRP and ASDAS), with the BASFI scores, which reflect disease severity indicated by impaired physical functions and with the sCTX levels.

Table 1 Characteristics of ankylosing spondylitis patients and controls

<table>
<thead>
<tr>
<th></th>
<th>Group I (n = 17)</th>
<th>Group II (n = 20)</th>
<th>Controls (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
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<tr>
<td>Range</td>
<td>21–42</td>
<td>24–44</td>
<td>23–44.5</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>30.6 ± 10.5</td>
<td>35.6 ± 8.8</td>
<td>33.7 ± 10.8</td>
</tr>
<tr>
<td>BMI</td>
<td>22.5 ± 5</td>
<td>21.1 ± 4.2</td>
<td>23.6 ± 2.2</td>
</tr>
<tr>
<td>Disease duration</td>
<td>3.2 ± 2.3</td>
<td>7.6 ± 2.3</td>
<td>–</td>
</tr>
<tr>
<td>ASDAS</td>
<td>2.9 ± 0.9</td>
<td>2.4 ± 0.9</td>
<td>–</td>
</tr>
<tr>
<td>BASFI</td>
<td>28.1 ± 2.3</td>
<td>34.9 ± 6.4**</td>
<td>–</td>
</tr>
<tr>
<td>mSASSS</td>
<td>16.5 ± 14.9**</td>
<td>23.35 ± 19.0</td>
<td>–</td>
</tr>
<tr>
<td>BMD (g/cm²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>0.87 ± 0.17*</td>
<td>0.92 ± 0.05*</td>
<td>1.016 ± 0.116</td>
</tr>
<tr>
<td>Osteopaenia (%)</td>
<td>47</td>
<td>35</td>
<td>–</td>
</tr>
<tr>
<td>Osteoporosis (%)</td>
<td>23.53</td>
<td>15</td>
<td>–</td>
</tr>
<tr>
<td>BMD (g/cm²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal femur</td>
<td>0.98 ± 0.05*,**</td>
<td>0.7 ± 0.15</td>
<td>1.027 ± 0.125</td>
</tr>
<tr>
<td>Osteopaenia (%)</td>
<td>35.3</td>
<td>45</td>
<td>–</td>
</tr>
<tr>
<td>Osteoporosis (%)</td>
<td>17.65</td>
<td>25</td>
<td>–</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>19 ± 16*</td>
<td>17 ± 13*</td>
<td>12.63 ± 1.36</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>9.0 ± 6.3*</td>
<td>8.8 ± 7.5*</td>
<td>1.79 ± 0.87</td>
</tr>
<tr>
<td>BALP (U/l)</td>
<td>26.6 ± 9.1</td>
<td>29.7 ± 11.2</td>
<td>22.8 ± 8.7</td>
</tr>
<tr>
<td>sCTX (ng/ml)</td>
<td>1.05 ± 0.77*</td>
<td>1.46 ± 0.67*</td>
<td>0.58 ± 0.05</td>
</tr>
<tr>
<td>Sclerostin (pmol/l)</td>
<td>69.5 ± 40.5*,**</td>
<td>45.5 ± 30.2*</td>
<td>99.7 ± 54.5</td>
</tr>
</tbody>
</table>

The values represent the mean ± SD.
ASDAS, Ankylosing Spondylitis Disease Activity Score; BALP, bone alkaline phosphatase; BASFI, Bath Ankylosing Spondylitis Functional Index; BMD, bone mineral density; ESR, erythrocyte sedimentation rate; mSASSS, modified Stoke Ankylosing Spondylitis Spine Score; sCTX, serum C-telopeptides of type I collagen.
*P<0.001 vs. controls.
**P<0.001 vs. group II.
Table 2 Correlations between bone mineral density, clinical, biochemical and laboratory parameters in ankylosing spondylitis patients (n = 37)

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Disease duration</th>
<th>ASDAS</th>
<th>BASFI</th>
<th>mSASSS</th>
<th>BMD Lumbar spine</th>
<th>BMD Proximal Femur</th>
<th>ESR</th>
<th>CRP</th>
<th>BALP</th>
<th>sCTX</th>
<th>Sclerostin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease duration</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>–</td>
<td>–</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>ASDAS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>–</td>
<td>–</td>
<td>NS</td>
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<td>NS</td>
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</tr>
<tr>
<td>BASFI</td>
<td>NS</td>
<td>NS</td>
<td>0.765*</td>
<td>NS</td>
<td>NS</td>
<td>–</td>
<td>–</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>mSASSS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>–</td>
<td>–</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>BMD Lumbar spine</td>
<td>NS</td>
<td>NS</td>
<td>–0.623*</td>
<td>NS</td>
<td>NS</td>
<td>–</td>
<td>–</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>BMD Proximal Femur</td>
<td>NS</td>
<td>NS</td>
<td>–0.459*</td>
<td>NS</td>
<td>NS</td>
<td>0.765*</td>
<td>–</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>ESR</td>
<td>NS</td>
<td>NS</td>
<td>0.912*</td>
<td>NS</td>
<td>0.769*</td>
<td>NS</td>
<td>–0.983*</td>
<td>–0.912*</td>
<td>–0.455*</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>CRP</td>
<td>NS</td>
<td>NS</td>
<td>0.769*</td>
<td>NS</td>
<td>0.912*</td>
<td>NS</td>
<td>–0.455*</td>
<td>0.4478</td>
<td>0.998*</td>
<td>–0.455*</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>BALP</td>
<td>NS</td>
<td>NS</td>
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<td>NS</td>
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<td>NS</td>
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<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>sCTX</td>
<td>NS</td>
<td>NS</td>
<td>–0.769*</td>
<td>NS</td>
<td>–0.770*</td>
<td>NS</td>
<td>–0.675*</td>
<td>–0.731*</td>
<td>–0.647*</td>
<td>–0.583*</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Sclerostin</td>
<td>NS</td>
<td>NS</td>
<td>–0.675*</td>
<td>–0.675*</td>
<td>–0.675*</td>
<td>NS</td>
<td>–0.675*</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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<td>NS</td>
</tr>
</tbody>
</table>

ASDAS, Ankylosing Spondylitis Disease Activity Score; BALP, bone alkaline phosphatase; BASFI, Bath Ankylosing Spondylitis Functional Index; BMD, bone mineral density; C-telopeptides of type I collagen; ESR, erythrocyte sedimentation rate; mSASSS, modified Stoke Ankylosing Spondylitis Spinal Score.

*Statistically significant correlation P<0.05.

In contrast, no correlation was demonstrated between a low BMD and each of mSASSS and levels of BALP and sclerostin.

The sCTX levels showed a negative correlation with the disease activity parameters, BASFI scores and low BMDs, whereas the BALP levels did not. No correlation was found between sCTX levels and mSASSS.

The sclerostin levels showed a negative correlation with the disease activity parameters (ESR, CRP and ASDAS), BASFI, sCTX and mSASSS (Table 2).

**Discussion**

AS is an inflammatory disease that predominantly affects the axial joints and intervertebral spaces. AS is characterized by a tight interplay between chronic inflammation and bone formation, which is only partly understood. Local inflammation appears to be crucial for bony proliferation along the periosteal and entheseal sites [18].

Although bone formation seems to be the cornerstone of the disease, AS is also associated with a systemic OP, which is a frequent complication, even in early stages of the disease, and is associated with elevated levels of biochemical markers of bone turnover, proinflammatory cytokines, and acute-phase reactants [19].

The context of defining disease duration has been much debated in the studies on AS, and at present the onset of first symptoms is considered to be the most important parameter [20]. We chose disease duration from the onset of symptoms because the long time that can elapse between symptoms and diagnosis can disturb the definition of early AS. We concurred with Karberg et al., [12] who defined disease duration as the ‘time since first symptoms’. An acceptably long delay between the onset of symptoms and the time of diagnosis for AS of about 8–11 [21] and 9.8–10.4 years has been reported [22].

Osteopaenia and OP of the lumbar spine were observed in 47 and 23.53% and in 35 and 15% patients in group I and II, respectively; however, they were observed in the proximal femur in 35.3 and 17.65% and in 45 and 25% of patients in group I and II, respectively. The patients had significantly lower BMDs compared with age-matched controls.

The prevalence of low BMDs ranges from 19 to 62% [9] and has been investigated in a few studies on early AS patients. Van Der Weijden et al. [23] reported a total prevalence of low BMD of 47% in the lumbar spine and hip among their study population [23]. Later, the same authors reported a high total prevalence of 51–54% for decreased BMD and of 13–16% for OP in an AS population, with a short disease duration in a systemic review, which coincides with our results [9]. Vasdev et al. [24] reported that OP of the spine and femoral neck was observed in 28.75 and 11.54% of patients, respectively. Other studies reported variable numbers for a prevalence of low BMDs in AS [8,12,25].

Our finding that hip BMDs were significantly lower in group II than in group I and that the BMDs of the lumbar spine showed an insignificant increase in the same patients clarifies that the hip is more reliable for measuring BMD in AS [19], as syndesmophytes give a false increase of spine BMDs, which is in agreement with the results of other authors [3,26,27].

There is an ongoing conflict of opinions about the association between BMD and disease activity variables such as ESR levels, CRP levels and ASDAS. Some studies failed to identify this relationship [28]. In contrast, many studies, including ours, confirmed the finding that a low BMD correlates with higher levels of parameters of disease activity in AS patients [8,10,11,23,29,30].
Grazio et al. [31] reported that this relationship was reflected more reliably at the proximal femoral sites than at the lumbar spine.

In our study, a high disease severity indicated by an impaired physical function (BASFI) appeared to be significantly associated with low BMDs, which coincides with the results of Van Der Weijden et al. [23], who reported this association in AS patients within 8 years of onset and also with the results of Kaya et al. [32] who highlighted the role of reduced mobility in OP. Nevertheless, mechanical factors, such as rigidity of the spine due to ankylosis, seem to be a less likely explanation for low BMDs in our patients because they were relatively young and had a short disease duration [23]. In contrast, we disagree with the results of Klingberg et al. [3], who failed to find a connection between low BMDs and BASFI scores and ASDAS.

The association between extensive syndesmophyte formation, restriction of spinal movement and OP has been demonstrated previously [3,12,23,33,34]. In our study, the total BMD did not show an association with mSASSS, probably because of early disease with minimal syndesmophyte formation, whereas it showed a correlation with hip BMD in group II. This confirms that hip BMD is more reliable compared with spine BMD [3,35] and can reflect the degree of syndesmophyte formation.

Assays for the proteins produced by osteoblasts, such as BALP and osteocalcin, have commonly been used to assess the degree of bone formation [36]. In addition, measurement of CTX-I levels is one of the most valuable assessments of osteoclastic activity [27]. Our patients showed a significant increase in sCTX levels compared with controls, with an insignificant difference among the two patient groups. In contrast, the BALP levels showed insignificant differences among the three groups.

The elevated sCTX levels correlated with the disease activity parameters and low BMD in our patients, confirming that inflammation is pivotal for bone loss in AS, which is in agreement with the results of Arends et al. [8]. Our results coincide with those of several previous studies reporting that increased bone degradation markers are associated with increased disease activity and loss of BMD in patients with AS [8,12,30,37]. Mitra et al. [38] reported that bone resorption parameters correlate with disease activity but not with BMD of the lumbar spine or femoral neck. Huang et al. [39] reported significantly higher levels of CTX in patients with syndesmophytes compared with those without it. Furthermore, sCTX levels were found to be reduced after initiating anti-TNF-α therapy, demonstrating an antosteoclastic effect [40].

The lack of a correlation between sCTX-I levels and mSASSS suggests that bone degradation (CTX-I) and proliferation (syndesmophytes measured by mSASSS) are not increased concurrently. It appears as if bone proliferation and degradation are uncoupled in AS [37].

Some authors reported that BALP levels in AS patients did not differ significantly from normal, with no correlation with the Bath Ankylosing Spondylitis Radiology Index (BASRI) scores or BMD [36,41], which coincides with our findings.

Sclerostin is expressed almost exclusively in bone [42,43], specifically by osteocytes, and is a key inhibitor of osteoblast activity, as it binds with LRP5/LRP6 and inhibits canonical Wnt signalling [44,45].

In the present study, we demonstrated reduced serum sclerostin level in AS patients, which were significantly lower in group II than in group I and in both groups compared with controls. Our findings concur with the result of, who reported that serum sclerostin levels are lower in AS patients compared with healthy controls [34]. In contrast, we disagree with the results of Taylan et al. [46], who reported similar sclerostin levels in patients and controls.

We demonstrated a negative correlation between sclerosis and each of mSASSS, disease activity parameters (ESR, CRP and ASDAS) and BASFI scores. This finding coincides with some studies that demonstrated that serum levels of sclerostin were correlated with syndesmophyte formation [12,34], and added that over time, sclerostin levels were significantly higher in AS patients without syndesmophyte growth compared with those with syndesmophyte growth [34]. Our results also agree with those of Saad et al. [47], who reported that persistent low sclerostin serum levels were restricted to the subgroup of patients with continuous high inflammatory parameters, suggesting that osteocyte dysfunction associated with AS was not reverted in these patients despite TNF blockage [47,48].

Interestingly, Dkk1 levels (which is another Wnt inhibitor) were significantly higher in patients with no syndesmophyte growth compared with those with syndesmophyte growth and were highly correlated with serum sclerostin levels [49].

Therefore, we can speculate that a low sclerostin expression could indeed increase the susceptibility for syndesmophyte formation, as Wnt inhibition will be impaired, allowing for more pathological new bone formation. Further, the close relation between sclerostin and inflammatory parameters has been established, evidenced by its gradual increase after anti-TNF-α therapy. Nevertheless, these levels remained lower than those observed in healthy individuals [47].

Circulating sclerostin levels were reported to be modestly associated with BMD and bone turnover [50], which is in disagreement with our results, in which no significant correlation was found between them.

Finally, no correlation was found between the clinical and laboratory parameters and between BMD and patient's age or disease duration. These findings are in agreement with those of Vasdev et al. [24], who reported that BMD was not influenced by total disease duration, whereas others stated that BMD depends on disease duration [12]. In contrast, we disagree with some
authors who demonstrated that in healthy adults sclerostin levels correlate positively with age [50,51,52] and that the decrease of BMD depends on disease duration [12].

**Conclusion**

A low BMD is common in early AS patients, and the role of inflammation seems to be pivotal in its pathogenesis. The monitoring of bone turnover markers and disease activity indices may help to predict patients at risk. Sclerostin expression is impaired in early disease and was linked to disease activity, bone turnover markers and increased structural damage, emphasizing the role of sclerostin in the pathogenesis of AS.

Prophylactic and therapeutic strategies are needed to fight bone loss in patients with AS. Further researches are highly recommended for the development of new therapies capable of preventing new bone formation early in the disease. Wnt pathway modulation seems to be the future therapeutic approach, yielding convenient results.

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Conflicts of interest

There are no conflicts of interest.

**References**


