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ORIGINAL RESEARCH

# Higher Level of Dickkopf-1 is Associated with Low Bone Mineral Density and Higher Prevalence of Vertebral Fractures in Patients with Ankylosing Spondylitis

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**Abstract** Patients with ankylosing spondylitis (AS) have an increased risk of bone loss and vertebral fractures. In this study, we explored the hypothesis that the excess bone loss and vertebral fractures might be related with the activity of the Wingless signaling pathway, and in particular with the serum levels of its circulating inhibitors, Sclerostin and Dickkopf-1 (DKK1). We recruited 71 patients diagnosed with AS. Lateral radiographs of the total spine were analyzed to detect the presence of vertebral fractures, and bone mineral density (BMD) was assessed in all patients using dual X-ray absorptiometry at lumbar spine and proximal femoral site. Blood samples were obtained and levels of C-reactive protein (CRP), DKK1, and Sclerostin were measured. Blood samples from 71 healthy sex- and age-matched volunteers were collected to be used as controls. Vertebral fractures were detected more commonly among men than in women (29 vs 8 %, respectively). DKK1, but not Sclerostin serum levels, were inversely correlated to lumbar spine *Z*-score BMD. Patients with one or more prevalent vertebral fractures had significantly higher DKK1 levels, without significant difference in Sclerostin serum levels. A significant positive correlation was found between DKK1 serum levels and CRP ($r = 0.240$, $p = 0.043$). The association we found between serum DKK1 levels and BMD values and vertebral fracture prevalence suggests that DKK1 might contribute to the severity of osteoporosis in AS.

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## Introduction

Ankylosing spondylitis (AS) is a chronic rheumatic disease characterized by inflammation and extensive remodeling of spine and joints. In contrast to rheumatoid arthritis, destructive changes are limited in AS, but extensive new bone formation results in the development of spinal syndesmophytes and extra-articular enthesophytes, leading to joint or spine ankylosis [1]. Parallel to the osteoproliferation, patients with AS also have an increased loss of bone, resulting in an elevated risk for vertebral fractures [2–4]. Low bone mineral density (BMD) values and bone loss were described at the spine and hip of patients with AS [5–10]. However, in advanced AS it may be difficult to interpret lumbar spine BMD as measured by dual-energy X-ray absorptiometry (DXA) in the anteroposterior projection, since the presence of syndesmophytes may lead to overesteem of the values, a problem not shared by the hip sites BMD. Risk factors for low BMD include disease severity as assessed by the Bath Ankylosing Spondylitis Radiology Index (BASRI), syndesmophyte score, modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS), inflammatory parameters, and markers of bone resorption [11–19]. Prevalence of osteoporosis of 19–62 % and of vertebral fractures of 9–42 % have been reported from different studies [2–4, 6, 12, 13, 16, 18, 20, 21]. Vertebral fractures are known to be associated with lower BMD in both the central and peripheral skeleton, advanced age, male gender, longstanding disease, impaired back mobility, syndesmophyte formation or mSASSS, disease activity, and peripheral joint involvement [19, 20, 22, 23].

The mechanisms in AS leading to both excess new bone formation and osteoporosis have been the object of a number of speculations and hypotheses. It was suggested that the wide range of excess bone formation might be related with the activity of the Wingless signaling pathway (Wnt) [24, 25]. In particular, the Wnt/β-catenin pathway influences bone formation through effects on osteoblast number, maturation, and progenitor differentiation and these actions are opposed by various intracellular and secreted factors. The secreted Wnt antagonists, Sclerostin and Dickkopf-1 (DKK1), block Wnt signaling by binding to Wnt co-receptors, low-density lipoprotein receptor-related protein 5 (LRP5) and 6 (LRP6), and by inhibiting the canonical Wnt/β-catenin signaling pathway [26, 27]. Sclerostin is a locally acting regulator of late osteoblast/preosteocyte differentiation [28, 29], and it is expressed by mature osteocytes. In adults, DKK1 it is almost exclusively confined to osteoblasts and maturing osteocytes [30]. Reduced expression of DKK1 in mice results in a high bone mass phenotype [31], and DKK1 may play a significant role in bone formation during diffuse idiopathic skeletal hyperostosis [32], while increased DKK1 levels are associated with osteolytic lesions in myeloma [33] and osteopenia [30, 34].

Low levels of local and circulating Sclerostin were reported in patients with AS compared with healthy individuals [35], while the results of DKK1 are inconclusive. The aim of this study is to examine a possible role played by the Wnt inhibitors DKK1 and Sclerostin in the prevalence of osteoporosis and vertebral fractures in AS patients.

## Materials and Methods

### Patients and Controls

Between January 2012 and March 2014 we recruited from our out-patients rheumatology center, 71 consecutive patients diagnosed with AS according to the modified New York criteria [36]. Fifty-nine were males (mean age 43 ± 12 years) and 12 were females (mean age 49 ± 12 years). Exclusion criteria were concomitant diseases with relevant impact on bone metabolism, like inflammatory bowel disease, clinical or laboratory evidence of hepatic, renal or bone metabolic diseases or treatment with drugs known to interfere with bone or mineral metabolism, including TNF-α blockers, glucocorticoids, and bisphosphonates. A careful case history was collected with particular attention to medication, together with anthropometric and demographic data. Disease duration was defined as time passed from onset of symptoms to recruitment. Disease activity and disability were assessed by Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Metrology Index (BASMI), and Bath Ankylosing Spondylitis Functional Index (BASFI). The presence of peripheral involvement was also recorded.

Blood samples from 71 healthy sex- and age-matched volunteers, mostly coming from hospital personnel or patients' relatives were collected to be used as controls.

### Radiography and Dual-Energy X-ray Absorptiometry (DXA)

Lateral radiographs of the spine were analyzed by a single radiologist in order to be scored for chronic AS-related changes [37] and to detect the presence of vertebral fractures. The presence of vertebral fracture was assessed by the Genant semi-quantitative method (at least 20 % reduction in anterior, middle, and/or posterior height) [38]. BMD was assessed in all patients using DXA (QDR Hologic Delphi) at lumbar spine (L1–L4), total hip, and femoral neck. The coefficient of variation was 1 % for spine and 1.2 % for femoral BMD. Measurements were expressed as *T*-score (difference in SD from the mean of a healthy young adult) and *Z*-score (number of SD above or below the mean for the patient's age, sex and ethnicity), considering the wide range of ages.

### Blood Tests

Blood samples were obtained in a fasting state from 8.00 to 9.30 AM. Levels of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were analyzed immediately by using standard laboratory techniques. Aliquots of serum sample were stored at −50 °C until needed for analysis. Serum DKK1 and Sclerostin were measured with an enzyme immunoassay (Biomedica Medizinprodukte GmbH & Co. KG, Wien, Austria) with sensitivities of 0.38 and 8.9 pmol/L and an intra-assay coefficients of variation of 7.3 and 5.6 %, respectively. Interassay variability was assessed in our laboratory on four separate occasions on four serum samples with values well within the normal range, and the coefficient of variation (CV) was 8.2 and 6.9 %, for DKK1 and Sclerostin, respectively. The clinical study was conducted in accordance with the ethics principles of the Declaration of Helsinki and was approved by the local ethics committee. Each enrolled patient signed the informed consent to participate in the study.

### Statistical Analyses

Descriptive statistics are presented as range, mean, and standard deviation (SD). Correlations between continuous variables has been tested using Pearson correlation coefficient and multivariate linear regression. Continuous variables were compared between groups using *t* test or

analysis of variance (ANOVA). Chi-square test was used for comparing categorical variables. All tests were 2-tailed and differences were considered statistically significant if $p < 0.05$. Calculations were made with a statistical software (SPSS vers. 13.0, Inc, Chicago, USA).

## Results

In control subjects, the mean age (47 ± 12 years), body mass index (26.1 ± 4.3 kg/m$^2$), and gender distribution was similar to that of patients (results not shown).

The main clinical characteristics of male and female patients are listed in Table 1. 17 % of the patients were women and mean disease duration was 145 ± 111 months for men and 107 ± 96 months for women.

In Table 2, main clinical characteristics comparing patients with and without a vertebral fracture are shown. Vertebral fractures were detected more commonly among men than in women (29 vs 8 %, respectively). Most vertebral fractures were at least moderate (grade 2, 79 %), wedged, and affecting the final thoracic sites (T10–T12). When patients were ranked for severity according to BASMI or BASFI scores, the prevalence of vertebral fractures, corrected for age, was considerably higher in patients with more severe disease (Fig. 1). The prevalence of vertebral fractures in patients with disease duration ≤ or >120 months and mSASSS < or ≥15 was 18 or 32 %, and 5 or 34 %, respectively ($p < 0.05$).

**Table 1** The main clinical characteristics of male and female patients (*N*)

| | Men (59) | | Women (12) | | *p* |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| Age (years) | 43 | 12 | 49 | 12 | Ns |
| BMI (kg/m$^2$) | 26.5 | 4.2 | 25.2 | 3.0 | Ns |
| ESR (mm/h) | 13 | 11 | 23 | 15 | 0.009 |
| CRP (mg/L) | 4.9 | 6.4 | 6.0 | 7.1 | Ns |
| Lumbar spine *T*-score | −0.6 | 1.5 | −1.0 | 1.8 | Ns |
| Femoral neck *T*-score | −0.7 | 0,9 | −0.9 | 1.2 | Ns |
| Total hip *T*-score | −0.6 | 0.9 | −0.5 | 1.1 | Ns |
| Lumbar spine *Z*-score | −0.3 | 1.5 | −0.3 | 1.6 | Ns |
| Femoral neck *Z*-score | −0.1 | 0.9 | −0.2 | 1.0 | Ns |
| Total hip *Z*-score | −0.3 | 0.8 | −0.1 | 1.0 | Ns |
| mSASSS | 23 | 12 | 16 | 7 | 0.07 |
| Disease duration (months) | 145 | 111 | 107 | 96 | Ns |
| BASMI (score) | 2.4 | 2.0 | 1.3 | 1.4 | 0.07 |
| BASDAI (score) | 2.5 | 2.1 | 3.6 | 2.2 | Ns |
| BASFI (score) | 2.1 | 1.9 | 2.7 | 1.8 | Ns |

Ns = $p > 0.1$

The prevalence of patients with *Z*-score values ≤−2 was 14.5 % at the lumbar spine and 3 % at the hip. The BMD values in terms of *Z*-score (number of standard deviations above or below the mean for the patient's age, sex, and ethnicity) were not significantly different among fractured and non-fractured patients, with a trend for lower BMD values at total hip (−0.6 vs −0.2, respectively; $p < 0.1$).

Syndesmophytes were identified in 52 % of males and in 17 % of females, while peripheral joint involvement was observed in 15 and 42 %, respectively. We found a non-significant trend for lower *Z*-score values at total hip BMD in patients with syndesmophytes ($p = 0.10$), and lower spine BMD in patients with peripheral joint involvement as compared with those without ($p = 0.06$) (results not shown).

Serum Sclerostin was significantly lower in AS patients as compared to healthy controls (25.2 ± 9.4 vs 38.0 ± 17.2 pmol/L, respectively; Fig. 2) and it significantly correlated with age ($r = 0.241, p = 0.043$). DKK1 serum levels were also significantly lower in AS patients than in healthy controls (23.3 ± 13.1 vs 29.8 ± 15.9 pmol/L, respectively; Fig. 2), without significant correlation with age or disease duration. In Table 3, correlations between Sclerostin, DKK1, BMD, clinimetric parameters, and mSASSS are shown. DKK1 and Sclerostin levels were significantly and positively correlated in healthy controls (results not shown), but not among patients. DKK1, but not Sclerostin serum levels, were inversely correlated to lumbar spine *Z*-score BMD (Fig. 3) and positively with BASFI, BASMI score, and mSASSS. Patients with one or more prevalent vertebral fractures had significantly higher DKK1 levels (Fig. 4). A significant correlation was found between DKK1 serum levels and CRP ($r = 0.240, p = 0.043$).

## Discussion

Approximately a quarter of our relatively young AS patients exhibited a vertebral fracture; this proportion rose to a third of the patients in men. Prevalence of vertebral fractures of 9–42 % have been variably reported from different studies [2–4, 6, 12, 13, 16, 18, 20, 21], probably because different mean age or criteria of recruitment. The higher proportion of prevalent vertebral fractures in young men in comparison to age-matched women was observed also in the European general population [39, 40] and attributed to the increased risk of severe trauma in young men as compared with young women.

Most vertebral deformities were wedge fractures and affected the last thoracic tract: this might be attributed to the local biomechanical consequences of the presence of syndesmophytes, which are more common in this site [2].

The prevalence of vertebral fractures was more common in patients with more advanced or severe disease as

**Table 2** The main clinical characteristics in patients (*N*) with or without vertebral fractures

| | With fractures (18) | | Without fractures (53) | | *p* |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| Age (years) | 45 | 12 | 43 | 12 | Ns |
| BMI (kg/m$^2$) | 27.1 | 5.8 | 26.1 | 3.3 | Ns |
| ESR (mm/h) | 17 | 15 | 14 | 11 | Ns |
| CRP (mg/L) | 7.2 | 9.4 | 4.4 | 5.1 | Ns |
| Lumbar spine *T*-score | −0.6 | 1.5 | −0.6 | 1.5 | Ns |
| Femoral neck *T*-score | −1 | 0.9 | −0.6 | 0.9 | Ns |
| Total hip *T*-score | −0.9 | 0.7 | −0.5 | 0.9 | Ns |
| Lumbar spine *Z*-score | 0.3 | 1.7 | −0.3 | 1.5 | Ns |
| Femoral neck *Z*-score | −0.4 | 0.9 | −0.1 | 0.9 | Ns |
| Total hip *Z*-score | −0.6 | 0.7 | −0.2 | 0.9 | 0.09 |
| mSASSS | 30 | 11 | 18 | 10 | 0.000 |
| Disease duration (months) | 177 | 141 | 125 | 93 | 0.08 |
| BASMI (score) | 4 | 1.9 | 1.6 | 1.6 | 0.000 |
| BASDAI (score) | 2.9 | 1.7 | 2.6 | 2.3 | Ns |
| BASFI (score) | 3.6 | 1.7 | 1.8 | 1.8 | 0.001 |

Ns = $p > 0.1$

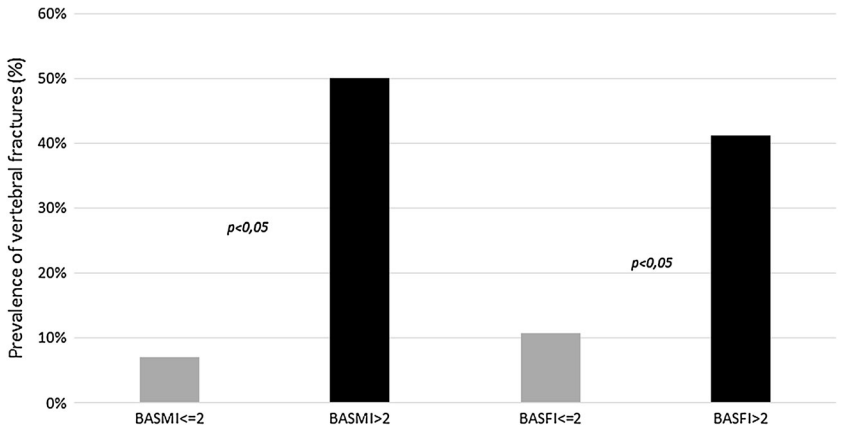


**Fig. 1** Prevalence of vertebral fractures in patients ranked for BASMI or BASFI scores

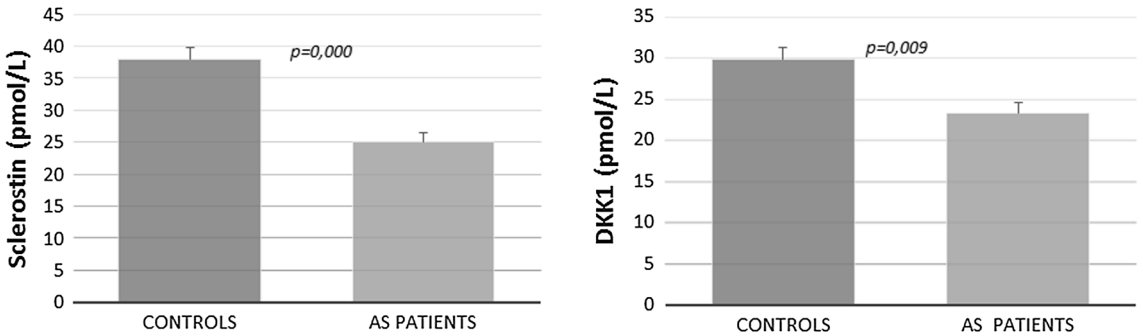


**Fig. 2** Mean (±SE) serum levels of Sclerostin and DKK1 in AS patients

assessed by BASMI and BASFI. However, we cannot exclude that the presence of vertebral deformities contributed to worse scores for both BASMI and BASFI, rather than the other way around. Indeed, the presence of vertebral fractures in patients with AS could seriously affect the clinimetric assessment, and it may explain the

**Table 3** Regression coefficients ($r$) and $p$ values among Sclerostin, DKK1, clinimetric parameters, mSASSS, and BMD $Z$-score

| | | DKK1 (pmol/L) | BASMI | BASFI | BASDAI | mSASSS | Lumbar spine $Z$-score | Femoral neck $Z$-score | Total hip $Z$-score |
|---|---|---|---|---|---|---|---|---|---|
| Sclerostin (pmol/L) | $r$ | .032 | −0.046 | 0.010 | 0.003 | 0.021 | −0.056 | 0.044 | −0.018 |
| | $p$ | 0.793 | 0.701 | 0.937 | 0.979 | 0.861 | 0.649 | 0.726 | 0.890 |
| DKK1 (pmol/L) | $r$ | 1 | 0.279 | 0.440 | 0.226 | 0.236 | −0.252 | −0.164 | −0.168 |
| | $p$ | | 0.019 | 0.000 | 0.058 | 0.048 | 0.036 | 0.188 | 0.185 |

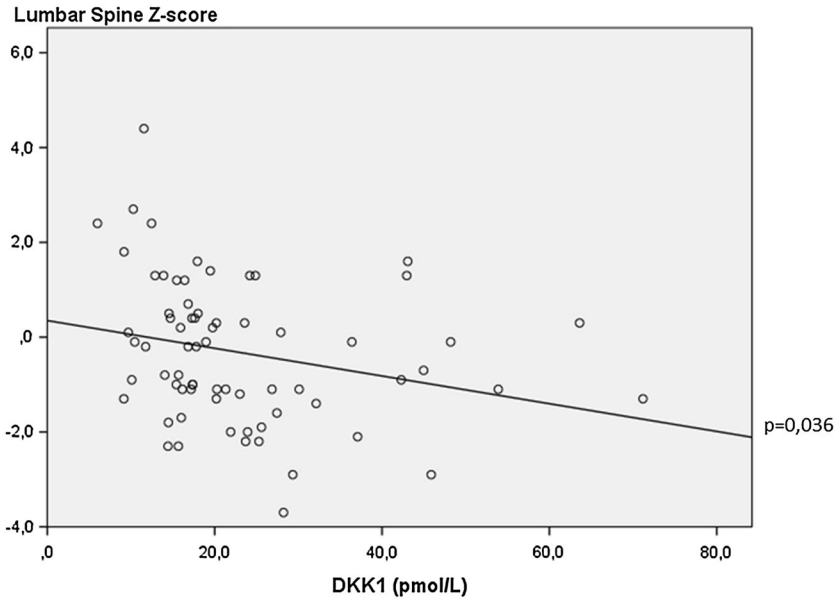


**Fig. 3** Correlation between DKK1 serum levels and lumbar $Z$-score BMD

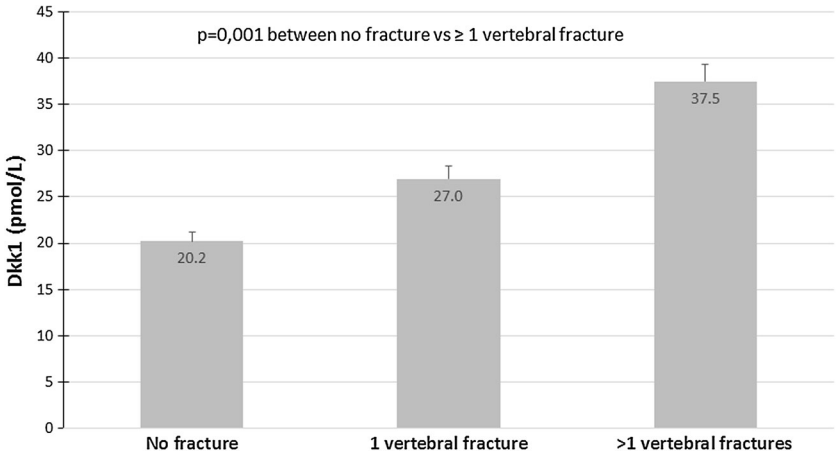


**Fig. 4** Mean (±SE) serum levels of DKK1 in AS patients without or with 1 or >1 prevalent vertebral fractures

partial responses of back pain to the specific treatment of AS [41].

The prevalence of patients with $Z$-score values $\leq -2$ was 14.5 % at the lumbar spine and only 3 % at the hip. Prevalence of low BMD or osteopenia/osteoporosis of 19–62 % has been variably reported from different studies, depending on the mean age and disease duration [42]. We found an un-significantly ($p < 0.1$) decreased prevalence of low hip BMD in fractured patients, but no relationship with spine BMD. Indeed, this was predictable since it is well known the overesteem of antero-posterior spine BMD values associated with the presence of syndesmophytes. Recent EULAR guidelines for the use of imaging in the assessment of osteoporosis in patients with syndesmophytes recommend the use of hip DXA [43].

Circulating Sclerostin was significantly lower in AS patients than in matched controls. Our results are in agreement with those reported by Saad et al. [44] and with an immunohistochemical study on surgical samples [35]. In the latter study, it was observed that Sclerostin expression is confined to osteocytes but it was virtually absent from AS tissue, as compared with samples from both patients with RA and healthy controls.

We found lower serum levels as compared with controls also of DKK1, the other inhibitor of the Wnt pathway. Our results are consistent with the observations of Kwon et al. [45] but at variance with another study where circulating DKK1 serum levels were found to be elevated [27]. However, in the latter study, the binding of DKK1 to cellular receptors was found impaired, suggesting that DKK1 might be dysfunctional in AS patients [27].

These observations of lower circulating levels of Wnt inhibitors suggest that Wnt-overexpression plays a relevant role in focal excess of bone formation in AS, with an additional contribution coming from the observation of increased serum levels of Wnt-3a [46]. On the other hand, in a longitudinal study it was reported with a decrease in the risk of syndesmophyte formation in patients with high DKK1 serum levels [47].

Interestingly, we found that DKK1 serum levels in AS patients are negatively correlated with *Z*-score of spine BMD and that higher serum levels of DKK1 are associated with a greater prevalence of 1 or more vertebral fractures. Thus in AS patients, serum DKK1, even though lower than in healthy controls, appears to be associated with an increased risk of severe osteoporosis. A negative correlation between serum DKK1 and BMD was recently reported also in postmenopausal women [48], elderly subjects [49], and in patients with rheumatoid arthritis [50]. This observation in AS-related osteoporosis is difficult to explain. It appears that osteoporosis in AS occurs despite focal stimulation of bone formation through the Wnt pathway. Probably the main pathogenesis of osteoporosis in AS should be searched elsewhere: immobilization, chronic inflammation, local biomechanical factors as Wolff's law. However, also higher DKK1 levels might contribute to the severity of osteoporosis in AS. A major determinant of DKK1 levels may be disease activity, because we found a positive correlation between DKK1 serum levels and CRP, thus concurring to explain the known association between disease activity and risk of osteoporosis [20].

It should be emphasized that there are several important limitations to this study. Primarily, it was designed as a cross-sectional study with a relatively small sample size. The authors recognize that the observed association between DKK1 and osteoporosis might not to mean a pathogenetic role. Thus, the results of this study need to be confirmed in prospective longitudinal studies. Moreover, other potential determinants of DKK1 serum levels should be investigated. Another important limitation is that the sample of AS patients included only mild forms (mean BASMI, BASFI and BASDAI around 2) since patients taking TNF inhibitors were excluded. This may also be responsible of a low prevalence of osteoporosis.

In conclusion, an important novelty coming from our study is the potential role played by DKK1 in the development of osteoporosis in AS: the observed association between serum DKK1 levels, BMD values, and vertebral fracture prevalence suggests that DKK1 might contribute to the severity of osteoporosis in AS.

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**Compliance with Ethical Standards**

**Conflict of Interest** Maurizio Rossini, Ombretta Viapiana, Luca Idolazzi, Francesco Ghellere, Elena Fracassi, Sonila Troplini, Maria Rosaria Povino, Vidya Kunnathully, Silvano Adami, and Davide Gatti declare that they have no conflict of interest.

**Human and Animal Rights and Informed Consent** The clinical study was conducted in accordance with the ethics principles of the Declaration of Helsinki and was approved by the local ethics committee. Each enrolled patient signed the informed consent to participate in the study.

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