



Low bone mineral density of vertebral lateral projections can predict spinal radiographic damage in patients with ankylosing spondylitis

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Abstract

Objectives To investigate the association between bone mineral status and spinal radiographic damage in patients with ankylosing spondylitis (AS) and determine whether bone mineral status can predict further spinal radiographic damage after 2 years.

Methods Bone mineral density (BMD) of the lumbar spine (anteroposterior and lateral projections), femoral neck, and total hip and trabecular bone score (TBS) of the lumbar spine were measured in AS patients ($n = 54$) who fulfilled the modified New York criteria. Spinal radiographic damage was scored on cervical and lumbar spine radiographs using modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) at baseline and after 2 years. Simple and multiple linear regression analyses were performed to examine predictors of spinal radiographic damage.

Results Patients with advanced AS exhibited low BMD on lumbar spine lateral projections, femoral neck, and total hip and low TBS. Low vertebral bone mass at baseline, assessed by BMD of the lateral projections or TBS, was independently associated with baseline mSASSS. After 2 years, mSASSS change from baseline was significantly associated with high baseline mSASSS, high baseline erythrocyte sedimentation rate and C-reactive protein (CRP) levels, and low baseline BMD of the lumbar spine lateral projections. The best predictive model for spinal radiographic progression consisted of baseline mSASSS, baseline CRP, and low BMD of lateral lumbar spine (area under curve = 0.826).

Conclusions BMD at vertebral lateral projections and TBS were inversely associated with baseline mSASSS in AS patients. Low BMD at vertebral lateral projections, as well as baseline mSASSS and inflammatory markers, might predict spinal radiographic damage in AS.

Key Points

- Vertebral bone mineral density of lateral projections and trabecular bone score are inversely associated with baseline mSASSS in patients with ankylosing spondylitis.
- Baseline mSASSS, inflammatory markers, and low vertebral bone mineral density might predict spinal radiographic progression in patients with ankylosing spondylitis.

Keywords Ankylosing spondylitis · Bone density · Disease progression · Osteoporosis

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Introduction

Ankylosing spondylitis (AS) is a chronic, inflammatory disease that mainly affects the sacroiliac joints and spine. Bone loss is frequently observed at the axial skeleton of patients with AS [1–4]. Patients with AS are at increased risk of vertebral fractures as a result of osteoporosis [5–8]. Therefore, proper assessment of bone mass is important in patients with AS to lower the risk of vertebral fractures, which decrease quality of life.

Bone mineral density (BMD) of the lumbar spine or hip is conventionally evaluated by dual-energy X-ray absorptiometry (DXA) in AS patients. BMD of the lumbar spine measured at the anteroposterior (AP) projection has

twice the precision that lateral projection in normal subjects [9]. However, in AS patients, lumbar spine BMD in the AP projection can be overestimated due to new bone formation at the vertebral margin, facet joints, or ligaments during the disease process. Various alternative methods for assessing the vertebral bone status of AS patients have been investigated. Areal BMD of lateral projections, volumetric BMD estimated by DXA, and quantitative computed tomography (QCT) appear useful for evaluating vertebral bone mass, regardless of spinal damage [1, 10–14]. A recent study also showed that trabecular bone score (TBS), which is used to assess bone microarchitecture, can identify risk of osteoporosis and vertebral fracture in AS [8].

Mechanisms of bone loss in AS are multifactorial and include spinal immobility, genetics, inflammation, disease activity, and medications [14–17]. Localized as well as systemic inflammation appears to contribute to trabecular bone loss in AS [1, 3, 18–22]. Paradoxically, vertebral bony overgrowth (syndesmophytes) develops in patients with AS, and inflammation can also influence syndesmophyte formation [23–25]. Radiographic spinal damage is found more commonly in patients with a longer disease duration, but bone loss is frequently found in patients with both early and late AS [26]. Bone loss and syndesmophyte formation appear to be related, but a causative relationship has not yet been proven.

The purpose of our study was to examine the association between bone mineral status and radiographic spinal damage in AS. Bone mineral status was assessed using DXA of lumbar spine AP projections, lateral projections, and proximal femur as well as TBS. In addition, we investigated whether vertebral bone mineral status can predict radiographic spinal damage after 2 years.

Materials and methods

Study population

We consecutively enrolled patients with AS who visited Seoul St. Mary's hospital from September 2015 to January 2016. Patients ≥ 19 years of age who fulfilled the modified New York criteria for diagnosis of AS were included in this study [27]. Patients with a history of thyroid or parathyroid disease, excessive alcohol uptake, or chronic renal disease were excluded. Informed consent was obtained from the study participants. This study was approved by the ethics committee of Seoul St. Mary's hospital, the Catholic University of Korea (KC15OISI0012) and was performed in accordance with the Declaration of Helsinki.

Assessment of bone mineral density

BMD of lumbar spine AP projections (vertebrae L1 to L4) and lateral projections (vertebrae L2, L3, and L2 to L3), femoral neck (left), and total hip (left) was evaluated by DXA (GE Healthcare Lunar, Madison, WI, USA). The BMD of the lateral projections of the lumbar vertebrae was measured without including the intervertebral disc and posterior spinal segment. Lateral lumbar spine BMD was measured with participants lying on their side with hips and knees flexed and pelvis aligned perpendicular to the margin of scanning table. Patient positioning was helped by using a positioner to support the head, knees, and pelvis. Grams per square centimeter (g/cm^2), as well as *T* score (compared with values of young adults of the same sex) and *Z* score (compared with values of adults of the same age and same sex), is reported for the AP lumbar spine, femoral neck, and total hip. BMD of the lateral lumbar spine is presented as g/cm^2 . Reproducibility of DXA represented as coefficient of variation is 1.0% for the lumbar spine AP projections, 5.3% for the lumbar spine lateral projections, 1.5% for the femur neck, and 0.9% for the total hip. Reference standard for *T* score is Asian population.

For individuals ≥ 50 years of age, World Health Organization definitions were used to determine osteopenia (*T* score < -1 to > -2.5 standard deviations [SD]) and osteoporosis (*T* score ≤ -2.5 SD) [28]. For individuals < 50 years of age, *Z* score ≤ -2 SD was considered to be below the expected range for age [29] and a *Z* score < -1 to > -2 SD was defined as subnormal [18]. Because *T* and *Z* scores for lateral lumbar spine BMD are not available, AP lumbar spine, femoral neck, and total hip BMD values were used to examine the prevalence of low BMD (osteopenia and osteoporosis for individuals ≥ 50 years of age; *Z* score < -1 to > -2 and *Z* score ≤ -2 for individuals < 50 years of age).

Assessment of trabecular bone score

TBS was extracted from DXA images of the AP lumbar spine using TBS iNSight® software (Version 2.0.0.1, Med-Imaps, Bordeaux, France). TBS (L1 to L4) is determined by using the same region of interest as the DXA lumbar spine, and evaluates the trabecular microarchitecture of the lumbar spine and provides information on bone quality [30]. $\text{TBS} \leq 1.35$ was considered to indicate a partially degraded or degraded microarchitecture [30].

Spine radiographs

Radiographic scoring of the cervical and lumbar spine was performed at baseline and after 2 years using the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) [31]. Lateral views of cervical and lumbar spine radiographs were used, and anterior edges of vertebrae from the lower border of

C2 to the upper border of T1 and from the lower border of T12 to the upper border of the sacrum were scored as follows: 0 = no abnormality; 1 = erosion, sclerosis, or squaring; 2 = syndesmophyte; 3 = bridging syndesmophyte (total score 0–72). mSASSS was determined by two experts blinded to the clinical information and if they disagreed on scores, the final score was reached by consensus. Mild, moderate, or advanced AS was determined based on baseline mSASSS: mild = mSASSS < 4; moderate = mSASSS \geq 4 to < 10; advanced = mSASSS \geq 10.

Demographic and clinical variables

Baseline characteristics such as age, sex, body mass index (BMI), disease duration, human leukocyte antigen-B27 positivity, serum erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) levels were examined as were current medications. Current medications included non-steroidal anti-inflammatory drugs (NSAIDs), sulfasalazine, methotrexate, tumor necrosis factor-alpha (TNF- α) inhibitors, glucocorticoids, bisphosphonate, and calcium/vitamin D.

Statistical analysis

Data are expressed as means (SDs) or medians (interquartile ranges, IQRs) for continuous variables and numbers (percentages) for categorical variables. BMD of the lumbar spine (AP and lateral projections), femoral neck, and total hip in addition to TBS of the lumbar spine are described according to the severity of AS (mild, moderate, or advanced AS). Differences in BMD or TBS among mild, moderate, and advanced AS patients were analyzed by the Jonckheere-Terpstra test. Differences between AP and lateral lumbar spine BMD (g/cm^2) according to groups with increasing numbers of syndesmophytes were also evaluated using the Jonckheere-Terpstra test. Spearman's correlation coefficients were calculated to assess the association between mSASSS and BMD or TBS. To examine whether baseline BMD can predict spinal radiographic damage after 2 years, simple and multiple linear regression analyses were used with setting the "mSASSS change over 2 years" as a dependent variable. Variables which had *p* values less than 0.2 in simple linear regression were included in multiple linear regression analysis (backward elimination method). ESR and CRP were considered separately in the multiple linear regression models to avoid multicollinearity. The best predictive model for spinal radiographic progression (defined as mSASSS change \geq 2 over 2 years) was selected using logistic regression analysis and receiver operating characteristic (ROC) curve analysis. All statistical analyses were performed using IBM SPSS Statistics 20.0 (IBM Corp., Armonk, NY, USA). *p* < 0.05 was considered statistically significant.

Results

Baseline characteristics of the study population

Fifty-four patients with AS were enrolled in this study. Mean (SD) age was 40.2 (9.1) years and 38 patients (70.4%) were men. Mean (SD) disease duration was 8.1 (6.6) years. Thirty patients (55.6%) had syndesmophyte(s) at baseline. Median (IQR) mSASSS was 7 (3–17) at baseline. Number (percentage) of patients who were taking medications at the time of the study is shown in Table 1.

Bone mineral status of the study population

BMD and TBS were measured in all study participants at baseline (Table 2). There was a discrepancy between AP and lateral lumbar spine BMD: mean AP lumbar spine BMD was $1.22 \text{ g}/\text{cm}^2$, whereas mean lateral lumbar spine BMD was $0.96 \text{ g}/\text{cm}^2$. Femoral neck and total hip BMD were as low as the lateral lumbar spine BMD. Mean TBS of the lumbar spine was 1.37.

Table 1 Baseline characteristics of the study population

	Total patients (<i>n</i> = 54)
Age, years, mean (SD)	40.2 (9.1)
Male sex, <i>n</i> (%)	38 (70.4)
BMI, kg/m^2 , mean (SD)	24.6 (3.6)
Disease duration, years, mean (SD)	8.1 (6.6)
HLA-B27-positive, <i>n</i> (%)	43 (82.7)
ESR, mm/h, median (IQR)	12.5 (6–25)
CRP, mg/dl, median (IQR)	0.23 (0.06–0.55)
mSASSS	
Median (IQR)	7 (3–17)
Mean (SD)	14.7 (18.7)
Number of syndesmophytes	
Median (IQR)	1 (0–5)
Mean (SD)	3.0 (4.3)
Presence of syndesmophytes, <i>n</i> (%)	30 (55.6)
Current medications, <i>n</i> (%)	
NSAIDs	49 (90.7)
Sulfasalazine	24 (44.4)
Methotrexate	3 (5.6)
TNF- α inhibitors	27 (50.0)
Glucocorticoids	1 (1.9)
Bisphosphonate	2 (3.7)
Calcium/vitamin D	8 (14.8)

HLA, human leukocyte antigen; BMI, body mass index; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; mSASSS, modified Stoke Ankylosing Spondylitis Spinal Score; NSAID, non-steroidal anti-inflammatory drug; TNF, tumor necrosis factor; SD, standard deviation; IQR, interquartile range

Table 2 Bone mineral density and trabecular bone score of the study population

	Total patients (<i>n</i> = 54)
BMD, g/cm ² , mean (SD)	
AP lumbar spine	1.22 (0.20)
Lat lumbar spine, L3	0.96 (0.29)
Lat lumbar spine, L2–3	0.96 (0.29)
Femoral neck	0.95 (0.18)
Total hip	0.97 (0.17)
Patients with osteopenia (WHO definition)* ^a or <i>Z</i> score < -1 to > -2 ^b , <i>n</i> (%)	
By AP lumbar spine	6 (11.1%)
By AP lumbar spine, femoral neck, or total hip	14 (25.9%)
Patients with osteoporosis (WHO definition) ^{†a} or <i>Z</i> score ≤ -2 ^{‡b} , <i>n</i> (%)	
By AP lumbar spine	5 (9.3%)
By AP lumbar spine, femoral neck, or total hip	10 (18.5%)
TBS, mean (SD)	
Lumbar spine	1.37 (0.12)
Patients with partially degraded/degraded bone microarchitecture (TBS < 1.35), <i>n</i> (%)	22 (40.7%)

BMD, bone mineral density; AP, anteroposterior; Lat, lateral; WHO, World Health Organization; TBS, trabecular bone score; SD, standard deviation

**T* score < -1 to > -2.5 SD; [†]*T* score ≤ -2.5 SD; [‡]below the expected range for age

^aFor patients ≥ 50 years of age; ^bfor patients < 50 years of age

Among all AS patients, 25.9% had osteopenia or a *Z* score < -1 to > -2.0 and 18.5% had osteoporosis or a BMD below the expected range for age (*Z* score ≤ -2). When using only BMD of the AP lumbar spine, the number of patients with osteopenia or a *Z* score < -1 to > -2.0 and osteoporosis or a BMD below the expected range for age was underestimated (11.1% and 9.3%, respectively).

BMD of the lateral lumbar spine showed a good correlation with the BMD of the femoral neck or total hip. BMD of the lateral lumbar spine (L3) was correlated with femoral neck BMD ($\rho = 0.491$, $p < 0.001$) and total hip BMD ($\rho = 0.432$, $p = 0.001$). BMD of the lateral lumbar spine (L2–3) was correlated with femoral neck BMD ($\rho = 0.566$, $p < 0.001$) and total hip BMD ($\rho = 0.504$, $p < 0.001$). TBS of the lumbar spine showed a modest correlation with BMD of femoral neck ($\rho = 0.387$, $p = 0.004$) and total hip ($\rho = 0.452$, $p = 0.001$).

Association between bone mineral status and mSASSS

Among 54 patients, 18 patients, 14 patients, and 22 patients had mild, moderate, and advanced AS, respectively. BMD of the lateral lumbar spine decreased significantly as the severity of spinal damage increased (Table 3). TBS of the lumbar spine decreased significantly according to the severity of damage. In contrast, BMD of the AP lumbar spine tended to increase as the severity of spinal damage increased. Difference between the AP and lateral BMD of the lumbar spine increased significantly as the number of syndesmophytes increased (Fig. 1).

mSASSS was negatively correlated with lateral lumbar spine BMD and lumbar spine TBS (Online Resource 1). mSASSS and femoral neck or total hip BMD were negatively correlated, but without statistical significance. Low vertebral bone mass assessed by DXA of lateral projections or TBS was significantly associated with mSASSS after controlling for variables such as age, sex, BMI, and CRP (data not shown).

Baseline BMD of lateral lumbar spine can predict spinal radiographic damage after 2 years

Among the 54 enrolled patients, 51 patients (94.4%) completed the 2-year follow-up radiographic spinal scoring. Baseline characteristics of patients who completed follow-up were similar to those of enrolled study population. Seventeen patients among 54 patients (31.5%) showed spinal radiographic progression (mSASSS change ≥ 2 over 2 years). Mean mSASSS change was 1.3 during the 2-year follow-up period.

Baseline ESR and CRP, baseline mSASSS, lateral BMD of L2 vertebrae, and TBS of lumbar spine were associated with mSASSS changes after 2 years based on univariable linear regression analyses (Table 4). ESR or CRP variables were included separately in the models of multivariable analyses. Multivariable-ESR model showed that baseline mSASSS and baseline ESR were associated with mSASSS changes. Multivariable-CRP model showed that lateral BMD of L2 vertebrae and baseline CRP were associated with mSASSS changes. High baseline ESR or CRP levels, high baseline mSASSS, and low baseline BMD of the lumbar spine at the

Table 3 Bone mineral density and trabecular bone score according to the spinal radiographic severity of ankylosing spondylitis

	Mild AS (n = 18) mSASSS < 4	Moderate AS (n = 14) mSASSS ≥ 4, < 10	Advanced AS (n = 22) mSASSS ≥ 10	p value
BMD, AP lumbar spine, g/cm ²	1.19 (0.16)	1.26 (0.21)	1.23 (0.21)	0.487
BMD, Lat lumbar spine, L2, g/cm ²	1.09 (0.29)	1.06 (0.31)	0.90 (0.28)	0.020
BMD, Lat lumbar spine, L3, g/cm ²	1.03 (0.28)	1.10 (0.30)	0.82 (0.22)	0.005
BMD, Lat lumbar spine, L2–3, g/cm ²	1.00 (0.32)	1.08 (0.27)	0.86 (0.24)	0.038
BMD, Femoral neck, g/cm ²	0.97 (0.21)	1.01 (0.19)	0.90 (0.12)	0.153
BMD, Total hip, g/cm ²	0.99 (0.19)	1.02 (0.20)	0.91 (0.11)	0.080
TBS, Lumbar spine	1.42 (0.10)	1.37 (0.09)	1.32 (0.13)	0.009

AS, ankylosing spondylitis; mSASSS, modified Stoke Ankylosing Spondylitis Spinal Score; BMD, bone mineral density; AP, anteroposterior; Lat, lateral; TBS, trabecular bone score

BMD and TBS values are expressed as mean (standard deviation)

lateral projections were predictors of spinal radiographic damage in patients with AS.

A predictive model for spinal radiographic progression

We made a best predictive model for spinal radiographic progression using variables of baseline mSASSS, baseline CRP, and low lateral BMD of L2 vertebrae (Fig. 2). Area under ROC curve was 0.826 (95% CI 0.698–0.954) from the model of baseline mSASSS, baseline CRP, and low lateral BMD of L2 vertebrae. The sensitivity and specificity of the model were 76.5% and 85.3%, respectively.

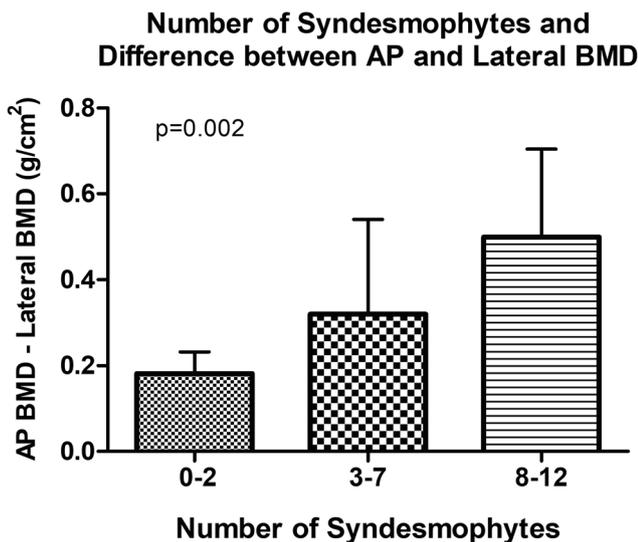


Fig. 1 The number of syndesmophytes and difference between anteroposterior and lateral lumbar spine bone mineral density. Data are expressed as mean and standard deviation

Discussion

This study showed that in patients with AS, there was a discrepancy between the BMD of lumbar spine AP projections and lateral projections. This difference might be due to the severity of spinal damage (syndesmophyte formation). Low vertebral bone mass as assessed by lateral BMD or TBS was independently associated with mSASSS. We also demonstrated that vertebral BMD, as assessed by lateral projection, might predict spinal radiographic damage in patients with AS after 2 years based on longitudinal mSASSS measurements. Other predictors of spinal radiographic damage were increased baseline mSASSS and increased levels of inflammatory markers at baseline.

Patients with AS had poor bone microarchitecture as well as low bone mass in our study. Bone loss was prominent in patients with advanced AS. These patients had lower TBS values than healthy individuals of a similar age and sex based on values reported in a previous study in Korea (mean TBS in the healthy population was 1.43) [32]. Femoral neck and total hip BMD values of patients with advanced AS were also lower than those of healthy individuals (mean BMD values of the femoral neck and total hip in the healthy population were 0.98 g/cm² and 1.03 g/cm², respectively) [32]. Prevalence of low BMD was 44.4% (prevalence of osteopenia or Z score < -1 to > -2 was 25.9% and prevalence of osteoporosis or Z score ≤ -2 was 18.5%) in our study. The prevalence of low BMD from AS patients was comparable with other reports from different cohorts or countries, although variations existed according to the definitions of low BMD [3, 4, 18, 33].

Assessing lumbar spine BMD using lateral projections and measuring TBS has several advantages compared with other methods such as volumetric BMD measured by QCT or DXA. QCT results in exposure of patients to higher levels of

Table 4 Predictors of spinal radiographic progression in patients with ankylosing spondylitis using linear regression analysis (dependent variable was mSASSS change over 2 years)

	Univariable		Multivariable-ESR		Multivariable-CRP	
	beta	p value	beta	p value	beta	p value
Age	0.199	0.162				
Male sex	0.154	0.282				
BMI	0.104	0.467				
Disease duration	0.107	0.457				
HLA-B27-positive	-0.045	0.758				
Log ESR	0.319	0.023	0.293	0.031		
Log CRP	0.291	0.038			0.309	0.022
Patients on NSAIDs	0.233	0.100				
Patients on TNF- α inhibitors	0.045	0.752				
Log baseline mSASSS	0.298	0.034	0.270	0.046		
Presence of syndesmophytes	0.214	0.131				
AP L1–4 BMD	-0.162	0.256				
Lateral L2 BMD	-0.292	0.038			-0.310	0.022
Lateral L3 BMD	-0.130	0.362				
Lateral L2–3 BMD	-0.144	0.312				
TBS	-0.289	0.039				

BMI, body mass index; HLA, human leukocyte antigen; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; NSAID, non-steroidal anti-inflammatory drug; TNF, tumor necrosis factor; mSASSS, modified Stoke Ankylosing Spondylitis Spinal Score; BMD, bone mineral density; TBS, trabecular bone score

Variables with a *p* value < 0.2 in univariable analyses were included in the multivariable linear regression analysis using a backward elimination method

radiation than DXA, and volumetric BMD estimated by DXA is not widely available. BMD of the lateral lumbar spine and

TBS can be obtained easily, and measurements are patient-friendly. BMD of the lateral lumbar spine can be measured readily using DXA. TBS of the lumbar spine is easily extracted from DXA images without the need for additional examinations. Thus, BMD of the lateral lumbar spine and TBS can be longitudinally followed-up to detect changes in bone mineral status.

Bone mineral status as assessed by vertebral BMD and TBS was significantly associated with spinal radiographic damage in patients with AS in the present study, suggesting that decreased bone mass may reflect the progression of spinal involvement in AS. Bone loss is one of the clinical phenomena that characterize the process of AS, although the causes of bone loss are not clear. There is some evidence that inflammation plays a role in bone loss of AS patients. Patients with persistent inflammation during follow-up were more likely to have decreased BMD, and patients who used TNF- α inhibitors had increased BMD [3, 18, 21]. Under inflammatory conditions, osteoclasts are activated (through induction of receptor activator of nuclear factor kappa B ligand) and osteoblasts are inhibited, leading to osteoporosis [34]. Likewise, studies have shown that bone turnover is higher in AS patients with bone loss than those without [33, 35]. New bone formation in AS is a site-specific process that is known to develop from vertebral corner fatty lesions which are associated with resolution of inflammation [36, 37].

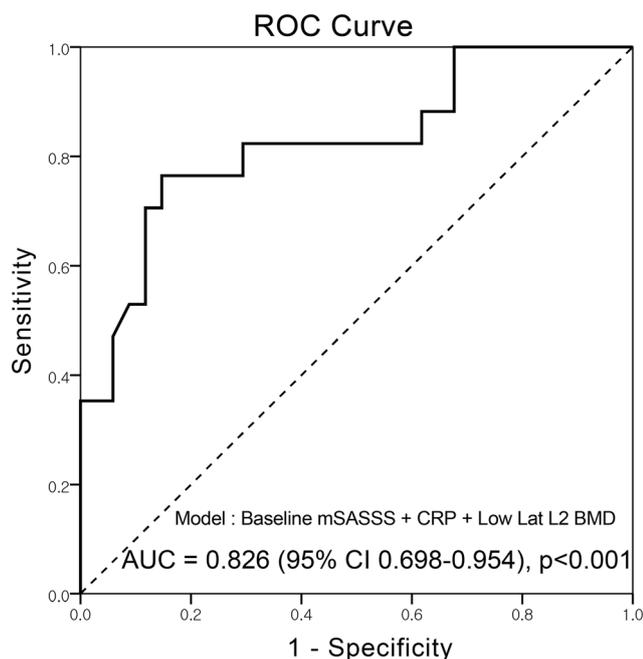


Fig. 2 Receiver operating characteristic curve of the predictive model for spinal radiographic progression (selected model = baseline mSASSS + baseline CRP + low baseline BMD of lateral lumbar spine L2). mSASSS, modified Stoke Ankylosing Spondylitis Spinal Score; CRP, C-reactive protein; BMD, bone mineral density

Several studies have examined the factors associated with spinal radiographic progression, and increased levels of inflammatory markers are predictors, consistent with our findings [23, 38]. Although the mechanisms of bone loss and new spinal bone formation are not the same, they are linked and both are affected by inflammatory processes.

We found that low vertebral BMD is a predictor of spinal radiographic progression in patients with AS. This result was also recently confirmed by another cohort study of patients with axial spondyloarthritis that low BMD was an independent predictor of new syndesmophyte formation [39]. Both studies had demonstrated that spinal damage and low BMD at baseline were associated with spinal radiographic progression. The difference is that our cohort population was at more advanced stage than aforementioned study [39]. We enrolled patients with AS, not axial spondyloarthritis. Patients who had syndesmophytes at baseline were more common in our cohort (55.6%) than those in axial spondyloarthritis cohort (29%). The results of the present study indicate that BMD of vertebral lateral projections may be useful to evaluate osteoporosis and predict radiographic progression in patients with AS (who had more advanced spinal involvement). Additionally, we also demonstrated a predictive model consists of baseline mSASSS, baseline CRP, and low BMD of lateral lumbar spine, which showed good performance to predict spinal radiographic progression in patients with AS.

Our study has limitations. First, it included a relatively small number of participants from a single center. Further studies of larger numbers of patients in a multi-center setting are required to verify our findings. Second, lack of a control group to evaluate the degree of BMD and TBS in AS patients; however, BMD has *T* score and *Z* score which enable to compare the values with control population. Third, reproducible positioning of the patients (in a decubitus position) for DXA of lumbar spine lateral projections is difficult. Also, in lateral scans, L2 vertebral body could overlay with ribs and L4 with pelvic bone [40].

In conclusion, patients with AS showed decreased BMD and TBS, particularly those with advanced AS. Low vertebral bone mass was strongly associated with spinal radiographic damage at baseline. Additionally, low vertebral BMD may be a predictor of the 2-year progression of spinal damage in patients with AS. Lumbar spine BMD measured at the lateral projections has advantages compared with lumbar spine BMD measured using AP projections in terms of assessing vertebral bone mineral status, and can also be used as a tool to predict the progression of spinal radiographic damage.

Compliance with ethical standards Informed consent was obtained from the study participants. This study was approved by the

ethics committee of Seoul St. Mary's hospital, the Catholic University of Korea (KC15OISI0012) and was performed in accordance with the Declaration of Helsinki.

Disclosures None.

References

- Klingberg E, Lorentzon M, Mellstrom D, Geijer M, Gothlin J, Hilme E, Hedberg M, Carlsten H, Forsblad-d'Elia H (2012) Osteoporosis in ankylosing spondylitis - prevalence, risk factors and methods of assessment. *Arthritis Res Ther* 14:R108. <https://doi.org/10.1186/ar3833>
- van der Weijden MA, Claushuis TA, Nazari T, Lems WF, Dijkman BA, van der Horst-Bruinsma IE (2012) High prevalence of low bone mineral density in patients within 10 years of onset of ankylosing spondylitis: a systematic review. *Clin Rheumatol* 31:1529–1535. <https://doi.org/10.1007/s10067-012-2018-0>
- Wang DM, Zeng QY, Chen SB, Gong Y, Hou ZD, Xiao ZY (2015) Prevalence and risk factors of osteoporosis in patients with ankylosing spondylitis: a 5-year follow-up study of 504 cases. *Clin Exp Rheumatol* 33:465–470
- Magrey MN, Lewis S, Asim Khan M (2016) Utility of DXA scanning and risk factors for osteoporosis in ankylosing spondylitis—a prospective study. *Semin Arthritis Rheum* 46:88–94. <https://doi.org/10.1016/j.semarthrit.2016.03.003>
- Jun JB, Joo KB, Her MY, Kim TH, Bae SC, Yoo DH, Kim SK (2006) Femoral bone mineral density is associated with vertebral fractures in patients with ankylosing spondylitis: a cross-sectional study. *J Rheumatol* 33:1637–1641
- Klingberg E, Geijer M, Gothlin J, Mellstrom D, Lorentzon M, Hilme E, Hedberg M, Carlsten H, Forsblad-D'Elia H (2012) Vertebral fractures in ankylosing spondylitis are associated with lower bone mineral density in both central and peripheral skeleton. *J Rheumatol* 39:1987–1995. <https://doi.org/10.3899/jrheum.120316>
- Pray C, Feroz NI, Nigil Haroon N (2017) Bone mineral density and fracture risk in ankylosing spondylitis: a meta-analysis. *Calcif Tissue Int* 101:182–192. <https://doi.org/10.1007/s00223-017-0274-3>
- Kang KY, Chung MK, Kim HN, Hong YS, Ju JH, Park SH (2018) Severity of sacroiliitis and erythrocyte sedimentation rate are associated with a low trabecular bone score in young male patients with ankylosing spondylitis. *J Rheumatol* 45:349–356. <https://doi.org/10.3899/jrheum.170079>
- Del Rio L, Pons F, Huguet M, Setoain FJ, Setoain J (1995) Anteroposterior versus lateral bone mineral density of spine assessed by dual X-ray absorptiometry. *Eur J Nucl Med* 22:407–412
- Gilgil E, Kacar C, Tuncer T, Butun B (2005) The association of syndesmophytes with vertebral bone mineral density in patients with ankylosing spondylitis. *J Rheumatol* 32:292–294
- Mermerci Baskan B, Pekin Dogan Y, Sivas F, Bodur H, Ozoran K (2010) The relation between osteoporosis and vitamin D levels and disease activity in ankylosing spondylitis. *Rheumatol Int* 30:375–381. <https://doi.org/10.1007/s00296-009-0975-7>
- Ulu MA, Cevik R, Dilek B (2013) Comparison of PA spine, lateral spine, and femoral BMD measurements to determine bone loss in ankylosing spondylitis. *Rheumatol Int* 33:1705–1711. <https://doi.org/10.1007/s00296-012-2632-9>
- Klingberg E, Lorentzon M, Gothlin J, Mellstrom D, Geijer M, Ohlsson C, Atkinson EJ, Khosla S, Carlsten H, Forsblad-d'Elia H (2013) Bone microarchitecture in ankylosing spondylitis and the

- association with bone mineral density, fractures, and syndesmophytes. *Arthritis Res Ther* 15:R179. <https://doi.org/10.1186/ar4368>
14. Lee YS, Schlotzhauer T, Ott SM, van Vollenhoven RF, Hunter J, Shapiro J, Marcus R, McGuire JL (1997) Skeletal status of men with early and late ankylosing spondylitis. *Am J Med* 103:233–241
 15. Carter S, Lories RJ (2011) Osteoporosis: a paradox in ankylosing spondylitis. *Curr Osteoporos Rep* 9:112–115. <https://doi.org/10.1007/s11914-011-0058-z>
 16. Grazio S, Kusic Z, Cvijetic S, Grubisic F, Balenovic A, Nemcic T, Matijevic-Mikelic V, Punda M, Sieper J (2012) Relationship of bone mineral density with disease activity and functional ability in patients with ankylosing spondylitis: a cross-sectional study. *Rheumatol Int* 32:2801–2808. <https://doi.org/10.1007/s00296-011-2066-9>
 17. Obermayer-Pietsch BM, Lange U, Tauber G, Fruhauf G, Fahrleitner A, Dobnig H, Hermann J, Aglas F, Teichmann J, Neeck G, Leb G (2003) Vitamin D receptor initiation codon polymorphism, bone density and inflammatory activity of patients with ankylosing spondylitis. *Osteoporos Int* 14:995–1000. <https://doi.org/10.1007/s00198-003-1501-5>
 18. Deminger A, Klingberg E, Lorentzon M, Geijer M, Gothlin J, Hedberg M, Rehnberg E, Carlsten H, Jacobsson LT, Forsblad-d'Elia H (2017) Which measuring site in ankylosing spondylitis is best to detect bone loss and what predicts the decline: results from a 5-year prospective study. *Arthritis Res Ther* 19:273. <https://doi.org/10.1186/s13075-017-1480-0>
 19. Maillfert JF, Aho LS, El Maghraoui A, Dougados M, Roux C (2001) Changes in bone density in patients with ankylosing spondylitis: a two-year follow-up study. *Osteoporos Int* 12:605–609. <https://doi.org/10.1007/s001980170084>
 20. Kang KY, Lee KY, Kwok SK, Ju JH, Park KS, Hong YS, Kim HY, Park SH (2011) The change of bone mineral density according to treatment agents in patients with ankylosing spondylitis. *Joint Bone Spine* 78:188–193. <https://doi.org/10.1016/j.jbspin.2010.05.010>
 21. Li H, Li Q, Chen X, Ji C, Gu J (2015) Anti-tumor necrosis factor therapy increased spine and femoral neck bone mineral density of patients with active ankylosing spondylitis with low bone mineral density. *J Rheumatol* 42:1413–1417. <https://doi.org/10.3899/jrheum.150019>
 22. Sarikaya S, Basaran A, Tekin Y, Ozdolap S, Ortancil O (2007) Is osteoporosis generalized or localized to central skeleton in ankylosing spondylitis? *J Clin Rheumatol* 13:20–24. <https://doi.org/10.1097/01.rhu.0000255688.83037.42>
 23. Deminger A, Klingberg E, Geijer M, Gothlin J, Hedberg M, Rehnberg E, Carlsten H, Jacobsson LT, Forsblad-d'Elia H (2018) A five-year prospective study of spinal radiographic progression and its predictors in men and women with ankylosing spondylitis. *Arthritis Res Ther* 20:162. <https://doi.org/10.1186/s13075-018-1665-1>
 24. Chiowchanwisawakit P, Lambert RG, Conner-Spady B, Maksymowych WP (2011) Focal fat lesions at vertebral corners on magnetic resonance imaging predict the development of new syndesmophytes in ankylosing spondylitis. *Arthritis Rheum* 63:2215–2225. <https://doi.org/10.1002/art.30393>
 25. Maksymowych WP, Morency N, Conner-Spady B, Lambert RG (2013) Suppression of inflammation and effects on new bone formation in ankylosing spondylitis: evidence for a window of opportunity in disease modification. *Ann Rheum Dis* 72:23–28. <https://doi.org/10.1136/annrheumdis-2011-200859>
 26. Karberg K, Zochling J, Sieper J, Felsenberg D, Braun J (2005) Bone loss is detected more frequently in patients with ankylosing spondylitis with syndesmophytes. *J Rheumatol* 32:1290–1298
 27. van der Linden S, Valkenburg HA, Cats A (1984) Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum* 27:361–368
 28. Kanis JA (1994) Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: synopsis of a WHO report. WHO study group. *Osteoporos Int* 4:368–381
 29. Gordon CM, Leonard MB, Zemel BS (2014) 2013 pediatric position development conference: executive summary and reflections. *J Clin Densitom* 17:219–224. <https://doi.org/10.1016/j.jocd.2014.01.007>
 30. Silva BC, Leslie WD, Resch H, Lamy O, Lesnyak O, Binkley N, McCloskey EV, Kanis JA, Bilezikian JP (2014) Trabecular bone score: a noninvasive analytical method based upon the DXA image. *J Bone Miner Res* 29:518–530. <https://doi.org/10.1002/jbmr.2176>
 31. Creemers MC, Franssen MJ, van't Hof MA, Gribnau FW, van de Putte LB, van Riel PL (2005) Assessment of outcome in ankylosing spondylitis: an extended radiographic scoring system. *Ann Rheum Dis* 64:127–129. <https://doi.org/10.1136/ard.2004.020503>
 32. Kang KY, Goo HY, Park SH, Hong YS (2018) Trabecular bone score as an assessment tool to identify the risk of osteoporosis in axial spondyloarthritis: a case-control study. *Rheumatology (Oxford)* 57:587. <https://doi.org/10.1093/rheumatology/kex431>
 33. Arends S, Spoorenberg A, Efte M, Bos R, Leijnsma MK, Bootsma H, Veeger NJ, Brouwer E, van der Veer E (2014) Higher bone turnover is related to spinal radiographic damage and low bone mineral density in ankylosing spondylitis patients with active disease: a cross-sectional analysis. *PLoS One* 9:e99685. <https://doi.org/10.1371/journal.pone.0099685>
 34. Davey-Ranasinghe N, Deodhar A (2013) Osteoporosis and vertebral fractures in ankylosing spondylitis. *Curr Opin Rheumatol* 25:509–516. <https://doi.org/10.1097/BOR.0b013e32832620777>
 35. Arends S, Spoorenberg A, Bruyn GA, Houtman PM, Leijnsma MK, Kallenberg CG, Brouwer E, van der Veer E (2011) The relation between bone mineral density, bone turnover markers, and vitamin D status in ankylosing spondylitis patients with active disease: a cross-sectional analysis. *Osteoporos Int* 22:1431–1439. <https://doi.org/10.1007/s00198-010-1338-7>
 36. Maksymowych WP, Elewaut D, Schett G (2012) Motion for debate: the development of ankylosis in ankylosing spondylitis is largely dependent on inflammation. *Arthritis Rheum* 64:1713–1719. <https://doi.org/10.1002/art.34442>
 37. Magrey MN, Khan MA (2017) The paradox of bone formation and bone loss in ankylosing spondylitis: evolving new concepts of bone formation and future trends in management. *Curr Rheumatol Rep* 19:17. <https://doi.org/10.1007/s11926-017-0644-x>
 38. Poddubnyy D, Haibel H, Listing J, Marker-Hermann E, Zeidler H, Braun J, Sieper J, Rudwaleit M (2012) Baseline radiographic damage, elevated acute-phase reactant levels, and cigarette smoking status predict spinal radiographic progression in early axial spondyloarthritis. *Arthritis Rheum* 64:1388–1398. <https://doi.org/10.1002/art.33465>
 39. Kim HR, Hong YS, Park SH, Ju JH, Kang KY (2018) Low bone mineral density predicts the formation of new syndesmophytes in patients with axial spondyloarthritis. *Arthritis Res Ther* 20:231. <https://doi.org/10.1186/s13075-018-1731-8>
 40. Larnach TA, Boyd SJ, Smart RC, Butler SP, Rohl PG, Diamond TH (1992) Reproducibility of lateral spine scans using dual energy X-ray absorptiometry. *Calcif Tissue Int* 51:255–258

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