Severity of Sacroiliitis and Erythrocyte Sedimentation Rate are Associated with a Low Trabecular Bone Score in Young Male Patients with Ankylosing Spondylitis

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ABSTRACT. ***Objective.*** To examine factors related to a low trabecular bone score (TBS) and the association between TBS and vertebral fractures in patients with ankylosing spondylitis (AS).

Methods. One hundred patients (all male, aged < 50 yrs) who fulfilled the modified New York criteria for the classification of AS were enrolled. The TBS and bone mineral density (BMD) were assessed using dual-energy X-ray absorptiometry. Clinical variables, inflammatory markers, and the presence of vertebral fractures were also assessed. Sacroiliitis grade and spinal structural damage were measured using the modified New York criteria and the Stoke Ankylosing Spondylitis Spine Score (SASSS).

Results. The mean TBS was 1.38 ± 0.13. The TBS showed a positive correlation with BMD at the lumbar spine, femoral neck, and total hip. TBS negatively correlated with SASSS, whereas BMD at the lumbar spine showed a positive correlation. A significant decrease in TBS values was observed in patients with spinal structural damage ($p = 0.001$). Univariate analysis identified disease duration, erythrocyte sedimentation rate (ESR), sacroiliitis grade, and SASSS as being associated with TBS. Multivariate analysis identified ESR and sacroiliitis grade as being independently associated with TBS ($p = 0.006$ and $p < 0.001$, respectively). Ten patients had morphometric vertebral fractures. The mean TBS was lower in patients with vertebral fractures than in age-matched patients without fractures ($p = 0.028$). Lower TBS predicted vertebral fractures (area under curve = 0.733, cutoff = 1.311).

Conclusion. The TBS in young male patients with AS is associated with the ESR and severity of sacroiliitis. The TBS may be useful as a tool for assessing osteoporosis in AS. (First Release January 15 2018; J Rheumatol 2018;45:349–56; doi:10.3899/jrheum.170079)

Key Indexing Terms:
TRABECULAR BONE SCORE
SACROILIITIS
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ERYTHROCYTE SEDIMENTATION RATE

Ankylosing spondylitis (AS) is a chronic inflammatory disorder that involves mainly the spine and sacroiliac joints. Osteoporosis of the spine and peripheral bones is common in AS. The increased risk of osteoporosis in AS is related to both systemic inflammation and decreased mobility[1]. Patients with AS are at high risk of vertebral fracture; the risk of clinical vertebral fracture is 1.9–3.3 higher than that in subjects without AS[2,3]. The combination of spinal rigidity (due to formation of syndesmophytes) and osteoporosis within trabecular bone contributes to this high rate of vertebral fracture[4].

It is unclear which imaging approach is most useful for diagnosing and monitoring osteoporosis in AS. To diagnose osteoporosis, bone strength (which reflects both bone

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quantity and bone quality) should be measured[5]. Dual-energy X-ray absorptiometry (DEXA) measurement of bone mineral density (BMD) at the hip and spine is most often used to establish or confirm a diagnosis of osteoporosis and to monitor patients[6]. Most data related to bone loss in patients with AS are based on studies using DEXA measurement of BMD.

One limitation of BMD is that it relates only to the density of bone, with no reference to bone quality (e.g., microarchitecture), which is a key determinant of bone strength[7]. DEXA-based BMD is a 2-dimensional approach and cannot distinguish between cortical and trabecular compartments. In AS, inflammation has a direct effect on the trabecular bone of the vertebrae, but not the cortical bone[8]. Therefore, BMD alone may lead to misinterpretation of inflammation-induced changes in bone strength in AS. Another limitation of BMD as measured by DEXA is that bony changes such as osteophytes can confound spinal measurements[9]. Syndesmophytes in patients with AS may also increase lumbar spine BMD as measured by DEXA[10], as do osteophytes in patients with spinal osteoarthritis (OA). Therefore, a major challenge is to develop a clinically available, noninvasive technology for the accurate clinical evaluation of bone microarchitecture in AS.

The trabecular bone score (TBS) is a novel method used to evaluate bone microarchitecture. It is a textural index that evaluates pixel grey-level variations in the lumbar spine DEXA image, thereby providing an indirect index of trabecular microarchitecture[11]. The TBS derived from DEXA images correlates with the 3-D microarchitecture variables measured by quantitative computed tomography (QCT)[12,13]. A previous study shows that TBS is not influenced by spinal osteophytes, which may lead to an overestimation of BMD among patients with lumbar spine OA[14]. Another recent study shows that TBS is not affected by syndesmophytes in patients with axial spondyloarthritis (SpA)[15].

To our knowledge, the risk factors associated with a low TBS in AS are unknown and no study has examined the association between TBS and vertebral fracture in patients with AS. Therefore, the aims of our present study were to identify the factors related to a low TBS in patients with AS and to examine the association between TBS and vertebral fracture.

MATERIALS AND METHODS

Study patients. This was a retrospective analysis of medical records obtained from Seoul Saint Mary's Hospital and Incheon Saint Mary's Hospital. The study enrolled patients with AS who fulfilled the modified New York criteria for the classification of AS[16] and were followed up at the 2 participating hospitals between January 2011 and December 2014. All patients were > 20 years of age. To exclude the effects of sex and age, only male patients and patients < 50 years old were included. Exclusion criteria included psoriasis, inflammatory bowel disease, reactive arthritis, thyroid or parathyroid disorders, and chronic renal or liver disease. The study was approved by the ethics committees of Seoul St. Mary's Hospital (XC13RIMI0129K) and Incheon St. Mary's Hospital, Catholic University of Korea (XC13RIMI0129O).

Clinical data. Clinical assessments included demographic data (age, age at the time of AS diagnosis, and HLA-B27 status). Height and weight were measured at the time of DEXA measurements, and were used to calculate body mass index. Inflammatory markers [C-reactive protein and the erythrocyte sedimentation rate (ESR)] were measured at the time of DEXA examination. Medications were also recorded, including nonsteroidal anti-inflammatory drugs, sulfasalazine, methotrexate, tumor necrosis factor inhibitors, calcium, and bisphosphonates. No patient received systemic glucocorticoids.

BMD measurements. Areal BMD was measured at the lumbar spine (L1 to L4) and left hip using DEXA (GEHC-Lunar Prodigy densitometer). All measurements were taken by experienced operators using the same machine and standardized procedures for participant positioning. BMD was measured at the lumbar spine (L1–L4) and the left hip (femoral neck and total proximal femur), and was expressed as the number of grams of bone mineral per square centimeter (g/cm^2), the number of SD above or below the mean for a healthy 30-year-old adult of the same sex and ethnicity as the patient (T score), and the number of SD above or below the mean for an age-matched normal adult of the same sex (Z score). A position statement by the International Society for Clinical Densitometry (ISCD) recommends that Z scores be calculated in females prior to menopause and in males younger than 50 years. According to the ISCD recommendations, a low BMD is defined as a Z score ≤ –2.0 SD (compared with the age-matched mean)[17]. Data were compared with the densitometer manufacturer's reference values.

TBS assessment. The TBS was analyzed using DEXA images of the lumbar spine (L1–L4). Lumbar spine DEXA images were reanalyzed in an operator-independent automated manner using TBS iNight software version 2.1 (Med-Imaps). The software uses the posterior-anterior images, including the BMD region of interest and edge detection; thus, the TBS is calculated over exactly the same region as the lumbar BMD assessment.

Radiographic scoring. Radiographs of the lumbar lateral spine and pelvis were obtained at the time of the DEXA test. Sacroiliitis was assessed by viewing images of the sacroiliac joint and was graded according to the New York criteria[16] by a reader blinded to the clinical details of the patients. Radiographic scoring in the lumbar spine related to AS was assessed using the Stoke Ankylosing Spondylitis Spine Score (SASSS). The SASSS was calculated by scoring the anterior and posterior vertebral corners of the lumbar spinal segments, from T12 lower to S1 upper, with each segment scored from 0 to 3 points as follows: 0 = normal; 1 = erosion, sclerosis, or squaring; 2 = syndesmophyte formation; and 3 = a bridging syndesmophyte[18]. Thus, total scores ranged from 0 to 72. The number of syndesmophytes was assessed using the SASSS.

Assessment of vertebral fracture. Vertebral fracture was assessed on lateral radiographs of the lumbar spine (T12–L4) using the standardized semiquantitative method described by Genant, *et al*[19] and defined as a ≥ 20% reduction in vertebral height. Grading was performed by 2 experienced investigators (K.Y. Kang and H.N. Kim), both of whom were blinded to the clinical details of the patients. There were few discrepancies, and the 2 investigators reached a consensus when these were found. The interobserver variability was calculated using Cohen's kappa value ($\kappa = 0.76$).

Statistical analysis. Statistical analyses were performed using SPSS (version 21.0; SPSS Inc.). Continuous data were expressed as the mean ± SD and categorical data as percentages. Normally distributed variables were compared using an independent t test, and nonnormally distributed variables were compared using the Mann-Whitney U test. The chi-square test was used to compare categorical variables. Clinical variables and BMD values were compared in subgroups across tertiles of TBS using chi-square tests for categorical variables and Kruskal-Wallis nonparametric tests for continuous data. Spearman correlation coefficient was used to analyze the correlation between variables. Multiple linear regression models were used to assess the association between TBS and clinical variables. All variables with a p value < 0.05 in univariate linear regression were incorporated as explanatory variables (stepwise method). A receiver-operating characteristic (ROC) curve was constructed using the discriminant TBS for vertebral fracture. $P < 0.05$ was considered statistically significant.

RESULTS

The clinical characteristics of the study patients are shown in Table 1. The mean age was 34 ± 8 years and duration after diagnosis of AS was 6 ± 5 years. The mean SASSS and sacroiliitis grade were 9.5 ± 16.0 and 3.1 ± 0.6. Forty-two patients had 1 or more syndesmophytes. Among 100 patients, 19 had low BMD at the lumbar spine, 14 at the femoral neck, and 27 at the total hip. Thirty-four patients had a low BMD at any site (lumbar spine, femoral neck, and/or total hip). The mean TBS at the lumbar spine was 1.38 ± 0.13.

TBS correlated with BMD values at the lumbar spine, femoral neck, and total hip (Table 2). TBS also correlated with the Z score at all sites. TBS showed a negative correlation with the grade of sacroiliitis. BMD at the lumbar spine correlated positively with SASSS and the number of syndesmophytes, whereas TBS showed a negative correlation. As for TBS, BMD at the femoral neck and total hip also showed a negative correlation with SASSS and number of syndesmophytes. A significant decrease in TBS values was observed in patients with spinal structural damage (p = 0.001), as shown in Figure 1. In contrast to TBS, BMD at the lumbar spine did not differ between the 2 groups.

Univariate analysis revealed that TBS was associated with disease duration, ESR, the grade of sacroiliitis, and the SASSS (Table 3). Multivariate analysis showed that ESR and the grade of sacroiliitis were independently associated with TBS (p = 0.006 and p < 0.001, respectively).

Among the 100 patients examined, 10 (10%) had morphometric vertebral fractures. Eleven vertebral fractures were identified in 10 patients: seven grade 1 fractures and four grade 2 fractures. Therefore, we compared the TBS and the SASSS between patients with vertebral fracture and age-matched patients without vertebral fracture (Table 4). The mean TBS was lower in patients with vertebral fracture (p = 0.028). However, the SASSS was higher in patients with vertebral fracture (p = 0.018). The ROC curve for TBS as a discriminator of vertebral fracture is shown in Figure 2. We identified the best cutoff for TBS as 1.311, which yielded a sensitivity of 60% and a specificity of 93% for vertebral fractures. The area under the ROC curve was 0.733 (95% CI 0.491–0.975).

Table 1. Patient characteristics stratified according to the lumbar trabecular bone score. Values are mean ± SD or n (%).

Characteristics	Total, n = 100
Age, yrs	34 ± 8
Age at AS diagnosis, yrs	27 ± 8
Disease duration, yrs	6 ± 5
Weight, kg	70 ± 11
Height, cm	171 ± 6
BMI, kg/m^2	23.7 ± 3.3
HLA-B27 positivity*	83 (83)
History of uveitis	27 (27)
ESR, mm/h	22.6 ± 23.9
CRP, mg/dl	1.6 ± 3.4
Grade of sacroiliitis on radiograph	3.1 ± 0.6
SASSS	9.5 ± 16.0
No. syndesmophytes^	2.4 ± 4.6
Presence of syndesmophytes^	42 (42)
NSAID	73 (73)
Sulfasalazine	43 (43)
TNF inhibitor	28 (28)
Calcium	17 (17)
Vitamin D	9 (9)
Bisphosphonate	15 (15)
BMD, g/cm^2	
Lumbar spine	1.18 ± 0.19
Femoral neck	0.94 ± 0.15
Total hip	0.95 ± 0.15
T score	
Lumbar spine	–0.5 ± 1.6
Femoral neck	–1.0 ± 1.2
Total hip	–1.1 ± 1.1
Z score	
Lumbar spine	–0.6 ± 1.5
Femoral neck	–0.8 ± 1.0
Total hip	–0.9 ± 1.0
Low BMD, Z score < –2.0 at any site	34 (34)
TBS, lumbar spine	1.38 ± 0.13

*Available for 89 patients. ^Measured at the anterior and posterior vertebral corners from T12 inferior to S1 superior. AS: ankylosing spondylitis; BMI: body mass index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; SASSS: Stoke Ankylosing Spondylitis Spine Score; NSAID: nonsteroidal antiinflammatory drugs; TNF: tumor necrosis factor; BMD: bone mineral density; TBS: trabecular bone score.

DISCUSSION

Our cross-sectional study of young male patients with AS revealed that the severity of sacroiliitis and the level of ESR were associated with a low TBS. The TBS was lower in patients with AS with spinal damage than in those without. The results also showed that AS patients with vertebral fracture had a lower TBS than those without.

Chronic inflammation of musculoskeletal structures leads to structural damage to bone tissue, as well as symptoms such as pain and stiffness. The bone tissue directly exposed to inflammation (osteitis) in AS is the trabecular bone of the vertebrae[8]. Patients with AS have a high prevalence of osteoporosis in the vertebral bodies and an increased risk of fracture[20,21,22], suggesting that chronic inflammation results in loss of trabecular bone mass. Disease activity in AS contributes to the rate of bone loss, and osteoporosis is considered a manifestation of the disease itself rather than a comorbidity[23].

A US National Institutes of Health consensus development panel defined osteoporosis as a skeletal disorder characterized by compromised bone strength, thereby predisposing a person to increased risk of fracture[5]. BMD as measured by DEXA is the gold standard for the diagnosis and management of osteoporosis. However, BMD accounts for only 60–80% of bone strength; a number of skeletal features other than BMD contribute to bone strength and fracture risk[24]. Bone

Table 2. Correlation between the TBS, BMD, and radiographic damage. Data are given as r coefficient.

Variable	TBS	Grade of Sacroiliitis	SASSS	Syndesmophytes
TBS	—	–0.375**	–0.323**	–0.305**
BMD, lumbar spine	0.282**	0.158	0.201*	0.239*
BMD, femoral neck	0.369**	–0.180	–0.261*	–0.211*
BMD, total hip	0.463**	–0.279**	–0.323**	–0.248*
Z score, lumbar spine	0.387**	0.108	0.154	0.252*
Z score, femoral neck	0.395**	–0.177	–0.104	–0.056
Z score, total hip	0.482**	–0.236*	–0.175	–0.076

*p < 0.05. **p < 0.01. TBS: trabecular bone score; BMD: bone mineral density; SASSS: Stoke Ankylosing Spondylitis Spine Score.

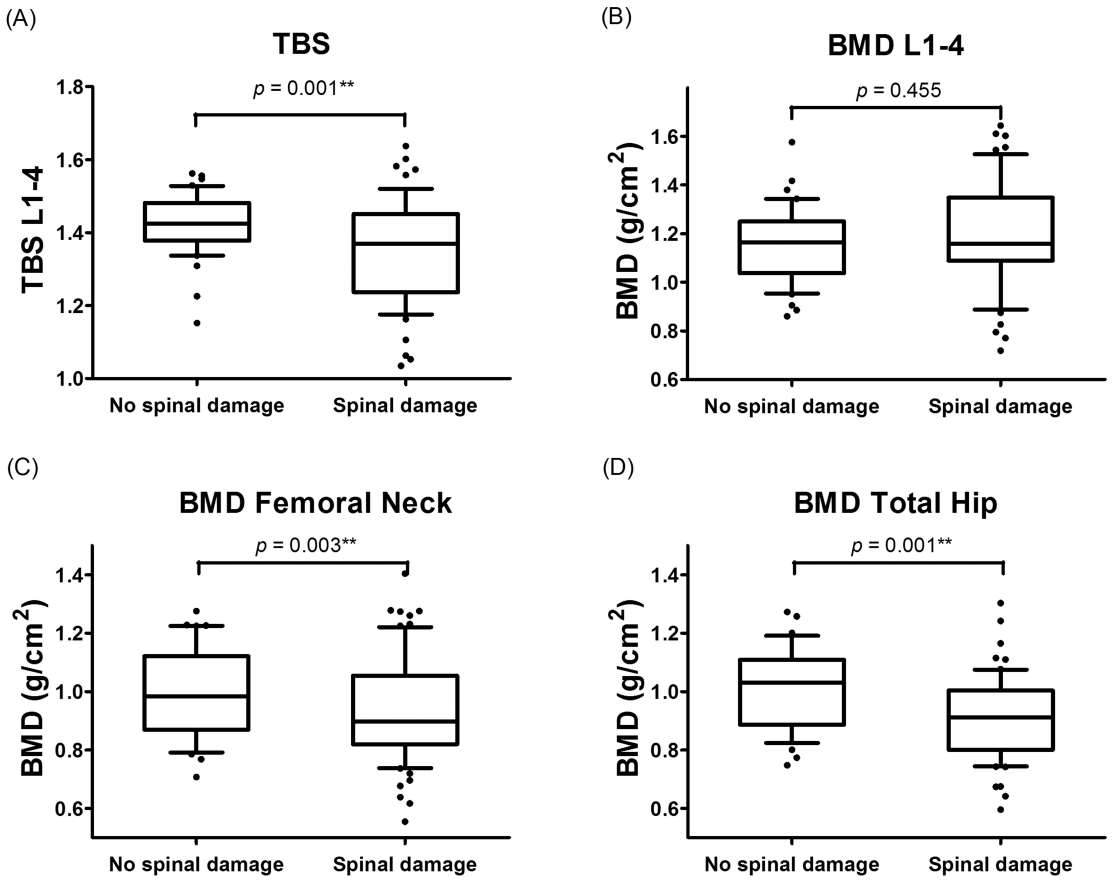

Figure 1. Comparison of (A) TBS and (B) BMD values at the lumbar spine, (C) BMD values at the femoral neck, and (D) BMD values at the total hip among patients with and without spinal structural damage. ** p < 0.05. TBS: trabecular bone scores; BMD: bone mineral density.

quality, as well as BMD, is involved in determining bone strength and predisposition to fracture. Bone quality is determined by bone microarchitecture, geometry, turnover, and mineralization[25]. The TBS is a recently developed analytical tool that performs grey-level texture measurements on lumbar spine DEXA images, thereby identifying information relating to trabecular microarchitecture. An earlier study showed that TBS correlates with the histomorphic trabecular microarchitecture of transiliac bone biopsies[26]. A low TBS is consistently associated with an increase in both the prevalence and incidence of fractures, and is partly independent of the clinical risk of fracture. In addition, TBS can predict fracture independently of fracture probability in the general population predicted using the FRAX algorithm[27]. A study showed that a low TBS is useful as a determinant of fracture risk, independent of BMD[28]. Also, osteophytes in cases of

Table 3. Linear regression analysis of the trabecular bone score in the lumbar spine.

Variables	Univariate Analysis			Multivariate Analysis		
	β	95% CI	p	β	95% CI	p
Age, yrs	–0.001	–0.930 to 0.002	0.355			
Yrs after AS diagnosis	–0.006	–0.011 to –0.002	0.006			
BMI	0.000	–0.007 to 0.008	0.900			
ESR	–0.001	–0.002 to 0.000	0.010	–0.001	–0.002 to –0.000	0.006
CRP	–0.005	–0.012 to 0.002	0.179			
Grade of sacroiliitis on radiograph	–0.074	–0.109 to –0.039	< 0.001	–0.075	–0.110 to –0.040	< 0.001
SASSS	–0.002	–0.003 to 0.000	0.032			
					$R^2 = 0.221$	

AS: ankylosing spondylitis; BMI: body mass index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; SASSS: Stoke Ankylosing Spondylitis Spine Score.

Table 4. Comparison of the TBS and spinal damage at the lumbar spine among patients with lumbar vertebral fracture and age-matched patients without fracture. Values are mean ± SD.

Variables	No Vertebral Fracture, n = 30	Vertebral Fracture, n = 10	p
TBS, L1–4	1.43 ± 0.08	1.31 ± 0.17	0.028
SASSS	7.2 ± 11.8	16.8 ± 16.5	0.018

TBS: trabecular bone score; SASSS: Stoke Ankylosing Spondylitis Spine Score.

spinal OA increase the overall BMD value in the lumbar spine, whereas TBS is not affected by such artifacts[14,29].

The European League Against Rheumatism makes the following recommendations regarding the use of imaging for the management of SpA: In patients with axial SpA without syndesmophytes in the lumbar spine on conventional radiography, osteoporosis should be assessed using hip DEXA and anterior-posterior spine DEXA; in patients with syndesmophytes in the lumbar spine on conventional radiography, osteoporosis should be assessed using hip DEXA supplemented by either spine DEXA (lateral projection) or possibly

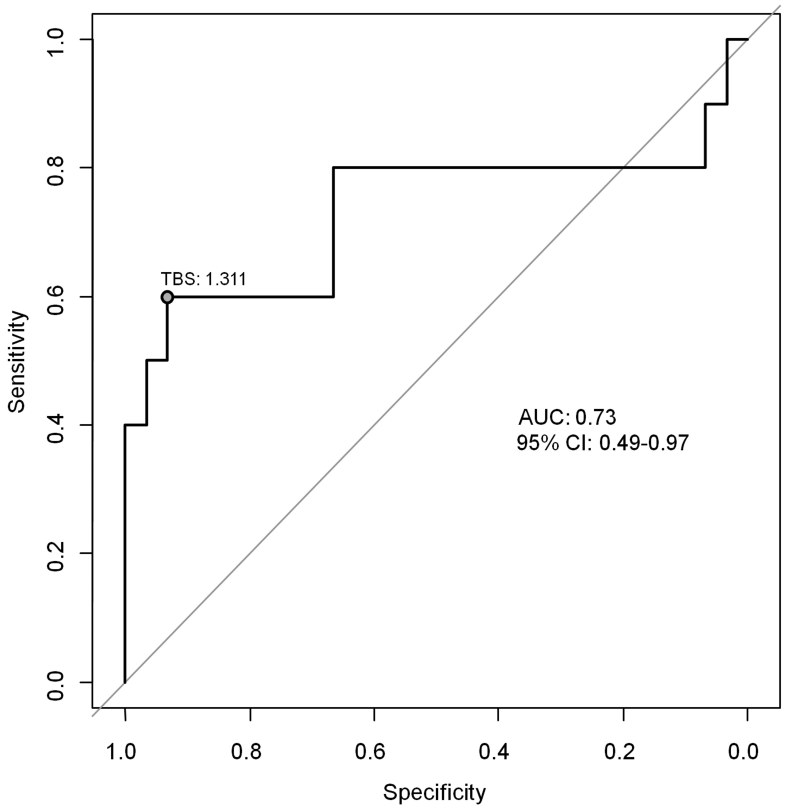

Figure 2. The ROC curve of the TBS used to discriminate vertebral fractures. ROC: receiver-operating characteristic; TBS: trabecular bone scores; AUC: area under the curve.

QCT of the spine[30]. Although spinal DEXA using a lateral view has the advantage of allowing selection of a trabecular zone in the center of the vertebral bodies, it has poor precision because of the difficulty in positioning the patients. Moreover, because of the overlap of the last rib and iliac crest, only L3 can be measured in some cases[14,31]. QCT cannot be performed routinely in a clinical setting because of the high radiation dose to the patient, the high cost, and limited access to such devices[27]. Therefore, a new tool that is unaffected by spinal damage is needed to assess osteoporosis and to predict fracture risk in AS.

The data presented herein suggest that the TBS is a useful tool for assessing osteoporosis in AS patients with spinal structural damage. BMD in the lumbar spine showed a positive correlation with spinal damage, while TBS showed a negative correlation with spinal damage and a positive correlation with BMD in the femoral neck and total hip. TBS was not affected by spinal structural damage in multivariate analysis. This is consistent with previous data from a study of axial SpA[15]. Taken together, these findings indicate that TBS as measured by DEXA, along with hip BMD, is a useful tool for assessing osteoporosis in AS, regardless of spinal structural damage.

The data presented herein also show that the ESR and the grade of sacroiliitis, which reflect the severity of cumulative inflammation, were independently associated with TBS after adjusting for confounding factors. Thus, TBS may reflect bone quality in the presence of chronic inflammation.

To the best of our knowledge, ours is the first study to examine the association between TBS and vertebral fracture in patients with AS. Low BMD is a strong risk factor for fractures in the general population[32], but previous studies of the association between low BMD and fracture in patients with AS are inconsistent[33,34,35,36]. This may be related to both an overestimation of BMD because of the presence of syndesmophytes and insufficient reflection of changes in the quality of trabecular bone caused by chronic inflammation. Here, AS patients with vertebral fracture had a lower TBS than age-matched patients without fracture. This suggests that a low TBS could be related to vertebral fracture in patients with AS. However, we did not analyze whether the TBS could predict development of vertebral fractures because this study was of cross-sectional design. Further longitudinal studies are required to examine whether the TBS is predictive of vertebral fracture.

The data presented herein also suggest that spinal structural damage may contribute to the development of vertebral fractures because of poor bone quality, as well as biomechanical effects resulting from poor spinal mobility and hyperkyphosis. We found that spinal structural damage was greater in AS patients with vertebral fracture than in those without. This is consistent with previous studies showing an association between spinal radiographic damage and vertebral fracture[34,37]. Stiffening of the spine in AS contributes to vertebral fracture risk by reducing biomechanical competence. We found that spinal structural damage was also related to a low TBS and poor bone quality, suggesting that spinal structural damage, as well as stiffening of the spine, may increase the risk of osteoporosis and may contribute to the development of vertebral fracture in AS. Additionally, the prevalence of vertebral fractures in our present study was higher than that reported previously[38]. The difference in the prevalence of vertebral fracture between the 2 studies may be related to patient characteristics. For example, our patients had more severe structural damage, which could associate with a greater frequency of vertebral fracture.

TBS has an advantage in that it directly assesses the microarchitecture of trabecular bone at the lumbar spine, which is the main area of involvement in patients with AS. A previous study showed that sacroiliitis on MRI correlated with BMD at the femoral neck and total hip; however, sacroiliitis on MRI was not associated with lumbar BMD[39]. Thus, bone loss at the spine in AS may be because of the localized effects of inflammation. Therefore, assessment of bone microarchitecture in the spine using the TBS may be a better predictor of the risk of osteoporosis and vertebral fracture in AS than high-resolution peripheral QCT of peripheral joints.

Our study has several limitations. First, it was of cross-sectional design; thus, although we could assess associations, we could not determine a cause-effect relationship. Another limitation was the use of the SASSS system to quantify spinal structural damage. This system is limited in that it takes into account structural changes in the lumbar spine with no consideration of the cervical or thoracic spines. Additionally, we had no data regarding the history of smoking and alcohol use. Despite the possible effects of smoking and alcohol on TBS, we did not evaluate them because of a lack of baseline information. Also, we did not evaluate the subclinical gut involvement. Gut inflammation is considered a risk factor for osteoporosis in AS[40]. Finally, we included only young male patients with AS. Further studies including women and older patients are needed to fully explore factors associated with TBS.

The lumbar TBS is associated with the ESR and the severity of sacroiliitis in young male patients with AS. The TBS is lower in patients with spinal structural damage and in those with vertebral fracture. A combination of the TBS and hip BMD may improve assessment of osteoporosis in AS patients with spinal structural damage.

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