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Disease Activity and Bone Microarchitectural Phenotype in Patients With Axial Spondyloarthritis

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Abstract

Background: Axial spondyloarthritis (AxSpA) is a chronic rheumatic disease characterized by spine inflammation, abnormal bone growth, and paradoxically osteoporosis and vertebral fractures. The pathogenesis of skeletal deficits in this disease is poorly understood. *Purpose*: We sought to evaluate volumetric bone mineral density (vBMD) and bone microarchitecture in patients with AxSpA and to identify disease-related factors associated with skeletal abnormalities. *Methods*: We enrolled patients between 2018 and 2021 as part of a 2-year prospective study at a single institution investigating skeletal health and the skeletal effects of interleukin-17 (IL-17) treatment. Patients with AxSpA who met Assessment in SpondyloArthritis International Society (ASAS) classification criteria by X-ray or had evidence of active inflammation on magnetic resonance imaging suggestive of sacroiliitis were referred to the study by their rheumatologists. We excluded those with a history of fragility fracture, multiple myeloma, Cushing's disease, primary hyperparathyroidism, osteomalacia, untreated vitamin D deficiency, secondary osteoporosis, or other systemic rheumatic diseases, as well as use of oral steroids for 2 or more weeks in the 6 months prior or current use of hormone replacement therapy, current oral bisphosphonate, past or current intravenous bisphosphonate, teriparatide, or denosumab therapies. A total of 1606 patients were screened for eligibility. Of these, 30 participants were enrolled (mean age 43 years, 50% male). Patients with AxSpA had dual-energy X-ray absorptiometry (DXA) measurements of areal BMD (aBMD) and high-resolution peripheral quantitative computed tomography (HR-pQCT) measurements of vBMD microarchitecture and failure load by finite element analysis. Standardized disease assessment tools used included the Bath Ankylosing Spondylitis Disease Activity (BASDAI), Metrology Index (BASMI), and Functional Index (BASFI). *Results*: In the 30 included patients, mean DXA and HR-pQCT Z-scores were within 1 standard deviation (SD) of normal for all indices, except for total vBMD in males (−1.2 SD below mean). Mean symptom duration was 11.7 years and mean scores for BASDAI, BASFI, and BASMI were 4.6, 3.6, and 2.7, respectively (range 1–10, 10 = severe limitation). Longer disease duration was associated with more severe skeletal deficits at the hip and tibia—specifically, lower hip aBMD, lower meta- and inner-trabecular vBMD, lower trabecular number, and higher trabecular separation and heterogeneity. *Conclusion*: This study of 30 patients with AxSpA found that abnormalities in bone density and microarchitecture at weightbearing sites were associated with longer disease duration. Because of its small sample size, larger studies are needed to better characterize the pathogenic disease factors that govern skeletal damage in AxSpA.

Keywords

bone mineral density, microarchitecture, axial spondyloarthritis

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Introduction

Axial spondyloarthritis (AxSpA) is an inflammatory rheumatic disease with an early onset (15–30 years old), defined by low back pain, stiffness, and radiographic damage to the sacroiliac joints and spine. Pathological structural damage to the spine is a hallmark of AxSpA, with abnormal bone growth bridging vertebral bodies and, paradoxically, loss of bone mineral density (BMD) and increased fragility [2]. Patients with AxSpA are at a significantly increased risk of

vertebral fracture [13,14,19]. In fact, rates of vertebral fracture in patients with AxSpA are nearly twice those of healthy individuals [25]. In rheumatoid arthritis, anti-tumor necrosis factor (TNF) therapy has been shown to decrease bone loss and increase bone formation after 6 months of therapy [28]. In psoriatic arthritis, anti-TNF therapy has been shown to arrest hand bone loss [16]. AxSpA is more frequently diagnosed in males than females, although inclusion of magnetic resonance imaging (MRI) findings for diagnosis has narrowed the male–female difference in incidence [21]. Clinical differences between the sexes for this disease have been described, including greater rate of radiological progression in males and higher disease activity scores and extra-articular manifestations in females [23]. Whether relationships between disease features and skeletal deficits differ among males and females is unclear.

Despite evidence of increased skeletal fragility, the standard tools for detecting osteoporosis have substantial limitations in the population with AxSpA. The combined effects of spinal and ligamentous ossification with syndesmophytes in AxSpA can contribute to inaccurately high spine aBMD measurements using dual-energy X-ray absorptiometry (DXA) [6,10,18,27]. Characterizing bone health in AxSpA is therefore challenging and may require advanced imaging techniques with selective measurements of trabecular and cortical bone to predict fractures and improve bone health [6,18].

Although increased bone fragility in patients with AxSpA is well recognized, its mechanism and associated factors remain poorly understood. Most prior studies investigating bone health in patients with AxSpA have utilized DXA. High resolution peripheral quantitative computed tomography (HR-pQCT) is a higher-order, 3-dimensional imaging technique that enables assessment of trabecular and cortical microstructure of peripheral bone sites. These peripheral measurements are closely related to strength and fragility at the spine [29,30].

The goal of this study was to use HR-pQCT to evaluate volumetric BMD and bone microarchitecture in patients with AxSpA and to identify the disease-related factors associated with skeletal abnormalities in this population. We hypothesized that HR-pQCT would detect skeletal abnormalities that were not apparent by DXA. Furthermore, we hypothesized that patients with worse disease activity and functional limitations would have lower BMD and worse microarchitecture. In addition, as AxSpA affects patient mobility, we postulated that relationships between disease features and skeletal abnormalities might be most pronounced at weightbearing sites.

Methods

Patients with AxSpA were enrolled between 2018 and 2021 as a part of a 2-year prospective study investigating skeletal health and the skeletal effects of interleukin-17 (IL-17) treatment. This report focuses on the cross-sectional evaluation of skeletal health and disease activity prior to initiation of IL-17 treatment. Patients at a single institution with AxSpA who met Assessment in SpondyloArthritis International Society (ASAS) classification criteria by X-ray (radiographic axial spondyloarthritis [SpA]) or had evidence (nonradiographic SpA) of active inflammation on magnetic resonance imaging (MRI) suggestive of sacroiliitis [7,12,22] were referred to the study by their rheumatologists. Exclusion criteria were history of fragility fracture, multiple myeloma, Cushing's disease, primary hyperparathyroidism, osteomalacia, untreated vitamin D deficiency (25 OH D$<$20 ng/mL), other forms of secondary osteoporosis, or other systemic rheumatic diseases, as well as use of oral steroids for 2 or more weeks in the 6 months prior or current use of hormone replacement therapy, current oral bisphosphonate, past or current intravenous bisphosphonate, teriparatide, or denosumab therapies. For patients with previous anti-tumor necrosis factor inhibitor (anti-TNF-i) therapy, enrollment was restricted until a washout period was completed (4 weeks for etanercept; 8 weeks for infliximab; 10 weeks for adalimumab, golimumab, or certolizumab; 6 months for ustekinumab). Patients under the age of 18 years and patients who were pregnant, nursing, or planning to become pregnant within 2 years were excluded. This protocol was approved by the Hospital for Special Surgery Institutional Review Board (IRB#2017-0660). Written informed consent was obtained from all participants included in the study.

Of 1606 patients screened for eligibility, 1377 were ineligible and excluded, most frequently for diagnosis of another rheumatic disease or for current anti-TNF-i therapy. A total of 186 were eligible but not approached based on the preference of their treating physician, 7 were eligible but declined participation, and 6 subjects withdrew after signing consent but before completing study procedures because they changed their mind. A total of 30 participants were enrolled. The cohort was predominantly white (70%), with mean age of 43 years; 50% were male (Table 1). Approximately half of the cohort (47%) was

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Table 1. Demographics of study patients.

Demographic characteristics[a]	Overall (N = 30)	Female (n = 15)	Male (n = 15)
Age (years, mean ± SD)	43 (14)	41 (13)	44 (15)
Sex, menopausal state			
Females, premenopausal	10 (33%)	10 (67%)	0 (0%)
Females, postmenopausal	4 (13%)	4 (27%)	0 (0%)
Females, perimenopausal	1 (3%)	1 (7%)	0 (0%)
Hispanic/Latino ethnicity	6 (20%)	5 (33%)	1 (7%)
Race			
White	21 (70%)	10 (67%)	11 (73%)
Black	4 (13%)	3 (20%)	1 (7%)
Asian	2 (7%)	0 (0%)	2 (13%)
Other	3 (10%)	2 (13%)	1 (7%)
Medical history			
Body mass index (mean ± SD)	28 (6)	26 (6)	29 (5)
Ever smoker	12 (40%)	4 (27%)	8 (53%)
Disease characteristics			
AxSpA symptom duration (years, mean ± SD)	11.7 (10.7)	9.0 (9.3)	14.4 (11.3)
HLA-B27 positive	14 (47%)	7 (47%)	7 (47%)
BASDAI (0–10) (units, mean ± SD)	5 (2)	4.4 (2)	5 (2)
BASFI (0–10) (units, mean ± SD)	4 (2)	**3 (2)**[b]	**4 (2)**
BASMI (0–4.4) (units, mean ± SD)	3 (1)	**2 (1)**[b]	**3 (1)**
m-SASSS (units, mean ± SD)[c]	11.7 (9.7)	6.55 (3.67)	17.1 (11.1)
Ankylosing Spondylitis Disease Activity Score (ASDAS)-CRP (units, mean ± SD)	3 (1)	3 (1)	3 (1)
Areal bone mineral density			
Trabecular bone score (TBS) (mean ± SD)	1.381 (0.133)	1.411 (0.102)	1.351 (0.155)
Lumbar spine (Z-score, mean ± SD)	−0.228 (1.879), n = 29	−0.427 (1.285)	−0.0143 (2.394), n = 14
Total hip BMD (Z-score, mean ± SD)	−0.170 (0.907), n = 28	0.030 (0.954)	−0.400 (0.826), n = 13
Femoral neck (Z-score, mean ± SD)	−0.230 (1.012), n = 28	−0.033 (1.204)	−0.458 (0.713), n = 13
1/3 radius (Z-score, mean ± SD)	−0.227 (1.163)	0.053 (1.232)	−0.507 (1.057)

BASDAI Bath Ankylosing Spondylitis Disease Activity; *BASFI* Bath Ankylosing Spondylitis Functional Index; *BASMI* Bath Ankylosing Spondylitis Metrology Index; *ASDAS* Ankylosing Spondylitis Disease Activity Score; *CRP* C-reactive protein; *TBS* trabecular bone score; *BMD* bone mineral density.

[a]Values represent number and proportion (%) unless otherwise noted.

[b]Bold values indicate a statistically significant difference between groups ($P < .05$).

[c]m-SASSS measurements (total score range 0–36) are calculated as 12 times the mean score of all scoring sites due to the absence of adequate cervical and lumbar X-ray films of each vertebra for each patient.

human leukocytic antigen (HLA) B27-positive. Disease-related impairment of function and mobility, measured as Bath Ankylosing Spondylitis Functional Index (BASFI) and Bath Ankylosing Spondylitis Metrology Index (BASMI), was higher in males than females (4 vs 3; 3 vs 2, respectively). Symptom duration was also longer in males than females (14 vs 9 years, respectively). More than half (57%) of the cohort reported vitamin D supplementation and 17% reported calcium supplementation. Nearly 1/3 (27%) reported use of prior biologic therapy (20% females, 33% males). Serum inflammatory markers, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) were within normal limits for most patients (~80%).

All participants completed surveys to ascertain information on demographics, calcium and vitamin D dietary intake and supplement use, and prior use of biologic medication (adalimumab, infliximab, golimumab, etanercept, ustekinumab, tocilizumab, or rituximab). Disease impact was assessed using standardized tools, BASFI, BASMI, and the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [5,11,17].

Serum measurement of HLA-B27, ESR, and CRP was obtained at the initial visit. Areal bone mineral density (aBMD) of the lumbar spine (L1–L4), total hip, femoral neck, and 1/3 radius were measured using DXA, Horizon A (S/N 201056) densitometer, Hologic, Inc. The *in vivo* precision of the measurements at our institution is 0.70% for the spine, 1.36% for the total hip, and 0.70% for the radius. The results were compared with those of individuals of the same age and sex from the Hologic healthy reference population to determine Z-scores. Trabecular bone score (TBS) parameters were calculated from the DXA images using TBS

iNsight software (Version 2.1; Medimaps Group). The TBS was determined as the average of the measurement for vertebrae L1–L4 [3,15]. A TBS value of ≥1.31 is considered normal and associated with the lowest risk of major osteoporotic fractures [8,24].

HR-pQCT scans were taken of the non-dominant distal radius and tibia using the Xtreme II scanner (Scanco Medical), except in cases of a prior fracture at the site or metal implant, in which case the contralateral limb was scanned. The Xtreme II utilizes a microfocus X-ray source (68 kVp voltage, 900 μA current, 43 ms integration time) to scan a 10.2-mm area along the axis of the long bone, resulting in a 60.7-μm isotropic voxel size. The region of interest was defined by a 2-dimensional scout view using a reference line placed at the distal end plate and a fixed offset of 9 mm for the radius and 22 mm for the tibia. All scans were performed and analyzed by a single highly trained operator and evaluated for motion with a score of 1 to 5; those who scored over 3 were excluded. The images were filtered and binarized using the manufacturer's standard method, and an automated segmentation algorithm was used to distinguish the cortical and trabecular regions [4]. The HR-pQCT measures assessed included total (Tt), trabecular (Tb), and cortical (Ct) area (Ar), volumetric BMD (vBMD), thickness (Th), trabecular number (Tb.N), separation (Tb.Sp), and cortical porosity (Ct.Po). The in vivo short-term reproducibility of these measures at the center is between 0 and 5% for all measures except cortical porosity [1]. Z-scores for HR-pQCT measures were generated based on comparisons to age- and sex-matched healthy controls, using the XCTII normative data from a Canadian cohort of 1236 people including 768 females and 468 males [32]. HR-pQCT data was used to calculate failure load using finite element analysis. Bone tissue was modeled as an isotropic, linearly elastic material with a Young's modulus (E_s) of 15 GPa and a Poisson's ratio of 0.3. A uniaxial displacement equaling 1% of the bone segment height was applied perpendicularly to the distal surface of the radius or tibia while the proximal surface was imposed with 0 displacement along the same direction.

Cervical and lumbar spine radiographs were evaluated using the modified Stoke Ankylosing Spondylitis Spine Score (m-SASSS), with a possible total score range of 0 to 72 [31]. Some spinal segments were not visible in all films, and images lacking more than 3 segments were excluded. Due to the absence of adequate cervical and lumbar X-rays for each patient, the score was calculated as 12 times the mean score of all scoring sites, with a possible score range of 0 to 36 [9].

Statistical Methods

All analyses were performed using SAS version 9.2 and SAS-STAT version 13.4. Descriptive statistics of patient demographics and clinical characteristics were performed, including mean and standard deviation (SD) for normally distributed continuous variables and proportions for categorical variables. *T*-tests and χ^2 tests were employed to determine differences in means and proportions between different groups, respectively. Spearman correlations were used to relate patient characteristics and imaging features from DXA and HR-pQCT. Variables of age, sex, AxSpA symptom duration, HLA-B27 status, and BASDAI, BASMI, BASFI scores were included in multiple regression models to generate slopes relating baseline predictors and bone microstructure indices.

Results

Mean aBMD Z-scores were within 1 SD of the age-matched reference mean for both females and males (Table 1). In females, aBMD measurements more than 1 SD below the reference mean were seen in 4 (27%) patients at lumbar spine, 2 (13%) patients at total hip, 4 (27%) patients at femoral neck, and 2 (13%) patients at 1/3 radius. In males, BMD measurements more than 1 SD below the reference mean were seen in 4 (29%) patients at lumbar spine, 3 (23%) patients at total hip, 2 (15%) patients at femoral neck, and 4 (27%) patients at 1/3 radius. There were no significant differences in bone density or microarchitectural parameters when the cohort was stratified by HLA-B27 status.

In the overall cohort, we found contrasting relationships between aBMD and TBS with disease characteristics, including BASMI and disease duration. Higher lumbar spine aBMD and TBS was associated with higher BASMI, an indicator of greater spinal mobility limitations, possibly reflecting artifact from disease impacting local BMD measurements at the spine. Conversely, higher BASMI was associated with lower TBS, a metric that may be less impacted by artifact from anatomic vertebral abnormalities. Longer disease duration was associated with lower aBMD at the hip (Fig. 1).

By HR-pQCT, longer disease duration was associated with more severe skeletal deficits at the tibia. Specifically, longer disease duration was associated with lower meta- and inner-trabecular vBMD (Fig. 2) and lower trabecular number (Fig. 3). Longer disease duration was also associated with higher trabecular separation and heterogeneity. Although disease duration was less strongly associated with microarchitectural features at the radius, we found that longer disease duration was associated with greater heterogeneity and cortical porosity. Overall, HR-pQCT measurements in female patients were similar to those of age-matched controls. In male patients, deficits were most pronounced in total and trabecular vBMD at the radius and in total vBMD at the tibia when compared with age-matched controls (Table 2).

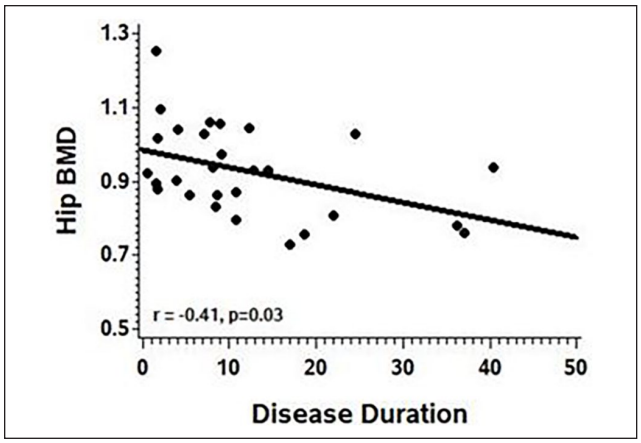

Fig. 1. Association between hip aBMD and disease duration by DXA.

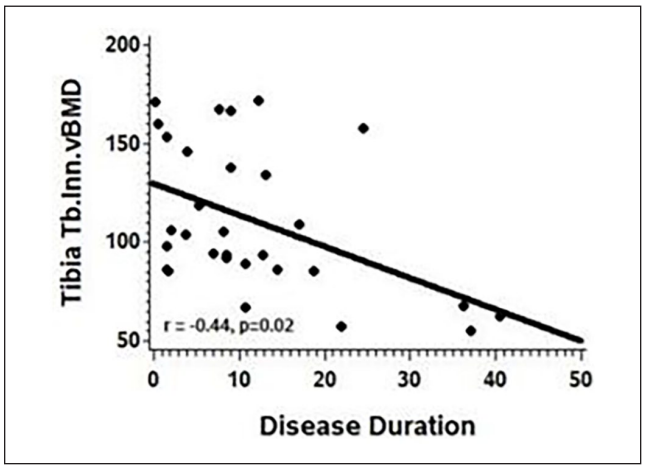

Fig. 2. Association between disease duration and tibia inner-trabecular vBMD.

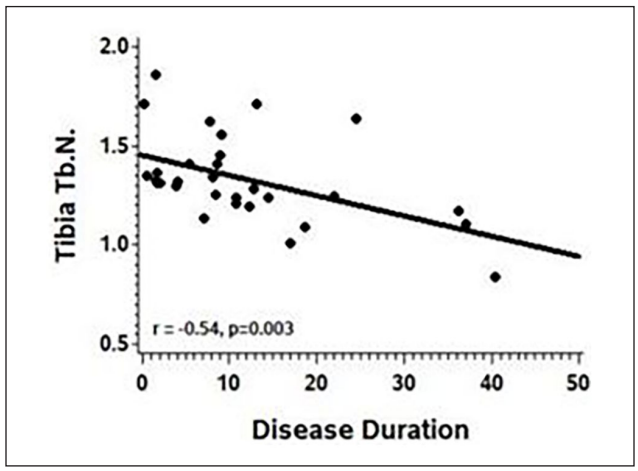

Fig. 3. Association between disease duration and tibia trabecular number.

Discussion

This study investigated the skeletal phenotype of a cohort of 30 patients with AxSpA and related disease features to skeletal abnormalities. Our cohort all had X-ray or MRI abnormalities and moderate disease activity, indicating a need to escalate or change therapy. Males in the cohort reported higher disease activity levels and longer disease duration than females. While bone density and microarchitecture appeared relatively preserved by both DXA and HR-pQCT overall, several relationships between duration of disease and bone abnormalities were found, particularly at weight-bearing sites. Our findings highlight the link between underlying disease and abnormal microarchitecture, providing a putative mechanism for skeletal fragility in AxSpA.

Our study has important strengths and limitations. This was a well characterized cohort, and we used strict eligibility criteria to identify participants and to exclude those with potential secondary causes of osteoporosis or who were using medications that might impact bone metabolism. However, these criteria may have contributed to a cohort with less bone disease than in the typical population with AxSpA. Although we excluded all current users of osteoporosis medications and applied a washout period for prior anti-TNF-i therapy, it is possible that prior medication use may have influenced bone phenotype. Another notable limitation is the small sample size. Larger numbers are required to further investigate whether sex and other patient characteristics modify the relationships between disease activity and skeletal indices. Our study was conducted at a single center, which may limit the generalizability of the results to a wider population. While our use of stringent enrollment criteria for patients with AxSpA enabled us to focus on a defined population, our results may not be representative of individuals with nonradiographic disease. This was a cross-sectional analysis, which does not provide information on the temporal changes in bone health over time. In addition, the study was conducted during the COVID-19 pandemic, which likely affected our participants' general activity levels and health behaviors.

Our study utilized HR-pQCT to non-invasively investigate skeletal microarchitecture and overcome limitations of using DXA for skeletal assessment in patients with AxSpA, including 2-dimensionality, false elevation of aBMD by syndesmophytes, and difficulty in patient positioning due to limited spinal mobility [23]. Overall, our study found that the bone microarchitecture was preserved in the majority of patients. Z-scores in our cohort were within 1 SD of the respective reference populations for most indices, which contrasts with findings of previous mixed-sex cohort studies [6,9,13,14,19,26,27]. The few prior studies utilizing HR-pQCT to assess bone microarchitecture in patients with AxSpA used an older version of the scanner with lower resolution and subsequently lesser

Table 2. Summary of HR-pQCT Z-scores in study participants by sex*.

HR-pQCT Feature	Overall (n = 29)	Female (n = 14)	Male (n = 15)
RADIUS	Z-Score (mean ±SD)	Z-Score (mean ±SD)	Z-Score (mean ±SD)
Total vBMD	−0.767 ± 1.195	**−0.311 ± 1.182**	**−1.192 ± 1.075**
Cortical vBMD	−0.269 ± 1.414	−0.078 ± 1.280	−0.446 ± 1.552
Cortical Area	−0.586 ± 1.060	−0.590 ± 1.167	−0.583 ± 0.991
Trabecular vBMD	−0.611 ± 0.818	**−0.198 ± 0.650**	**−0.997 ± 0.785**
Trabecular Area	0.419 ± 1.260	−0.090 ± 1.400	0.726 ± 1.070
Trabecular BV/TV	−0.420 ± 0.756	**−0.047 ± 0.628**	**−0.768 ± 0.713**
Cortical Thickness	−0.785 ± 1.209	−0.553 ± 1.281	−1.001 ± 1.138
Cortical Porosity	−0.122 ± 1.079	−0.323 ± 1.005	0.065 ± 1.147
Trabecular Number	0.081 ± 1.003	0.368 ± 0.808	−0.186 ± 1.116
Trabecular Thickness	−0.704 ± 0.791	−0.519 ± 0.617	−0.878 ± 0.912
Trabecular Separation	−0.025 ± 0.926	−0.366 ± 0.788	0.294 ± 0.955
	Overall (n = 30)	**Female (n = 15)**	**Male (n = 15)**
TIBIA	Z–Score (mean ±SD)	Z–Score (mean ±SD)	Z–Score (mean ±SD)
Total vBMD	−0.790 ± 1.256	**−0.241 ± 0.997**	**−1.339 ± 1.276**
Cortical vBMD	−0.115 ± 1.301	0.216 ± 1.170	−0.445 ± 1.380
Cortical Area	−0.248 ± 1.095	−0.160 ± 1.157	−0.336 ± 1.062
Trabecular vBMD	−0.650 ± 1.187	−0.302 ± 1.210	−0.998 ± 1.093
Trabecular Area	0.352 ± 1.207	**−0.130 ± 1.191**	**0.833 ± 1.050**
Trabecular BV/TV	−0.656 ± 0.903	−0.486 ± 0.771	−0.826 ± 1.017
Cortical Thickness	−0.287 ± 1.065	0.036 ± 1.065	−0.610 ± 0.996
Cortical Porosity	0.636 ± 1.032	0.358 ± 1.196	0.914 ± 0.783
Trabecular Number	−0.089 ± 1.144	0.081 ± 0.759	−0.259 ± 1.440
Trabecular Thickness	−0.894 ± 0.951	−0.802 ± 1.110	−0.986 ± 0.789
Trabecular Separation	0.077 ± 1.138	−0.072 ± 0.735	0.225 ± 1.447

*Bold values indicate a statistically significant difference between male and females ($P < .05$).

ability to discern features of microstructure. Our study is the first AxSpA study to utilize the latest HR-pQCT (Xtreme II) technology. The greater resolution of the scanner we utilized may have contributed to our disparate findings. Moreover, we compared HR-pQCT assessments with a newly available normative dataset, which allowed us to generate Z-scores for microarchitectural indices and provide an estimate of how our cohort compared with a large health reference population. An important aspect of our study was the strict enrollment criteria that were used to identify participants who were at low risk of fragility fractures and not using any osteoporosis medications, as this was necessary for our longitudinal study design. The exclusion of individuals at high risk of fragility fractures may have led to selection bias in our cohort of individuals with fewer bone abnormalities than the broader population of individuals with AxSpA.

We found that individuals with greater severity of disease, assessed by several metrics, had more skeletal abnormalities. Previous studies have found associations between worse peripheral bone microarchitecture and increasing m-SASSS, HLA-B27 negative status, lumbar osteoporosis, syndesmophytes, and vertebral fractures [20,27]. The relationships we observed between disease activity, duration, and peripheral skeletal abnormalities provide further evidence of the systemic skeletal effects of the disease. Interestingly, we found differences in the specific relationships between bone density, microarchitecture, and disease severity between weightbearing and non-weightbearing sites. Longer disease duration was associated with lower aBMD at the hip, as well as lower vBMD in the inner and outer trabecular compartments of the tibia. Longer duration was also associated with microarchitectural abnormalities at the tibia, lower trabecular number, and greater separation and heterogeneity. At the radius, we found greater disease duration to be associated with greater trabecular heterogeneity and porosity. It is conceivable that the tibial abnormalities we observed, which were more severe and associated with more pronounced microarchitectural abnormalities, reflect changes in our subjects' overall activity and mobility as a result of having AxSpA. As the tibia is weightbearing, the effects of decreased activity may be most apparent at that site. In contrast, the factors that contribute to

skeletal abnormalities at the radius may be multifactorial and less directly related to changes in activity.

In conclusion, we found that in a cohort of 30 patients with AxSpA, disease severity was related to low BMD and microarchitectural abnormalities. Specific relationships between disease duration and skeletal deficits were most pronounced at weightbearing sites. Furthermore, larger studies are needed to better characterize the mechanisms by which AxSpA impacts bone quality and the factors that govern susceptibility to and severity of skeletal damage in this condition.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: WY, MD, declares a relationship with Novartis. SMG, MD, reports relationships with UCB and Novartis. EMS, MD, reports a relationship with Radius Pharmaceuticals. The other authors declare no potential conflicts of interest.

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Human and Animal Rights

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent

Informed consent was obtained from all participants included in this study per the Hospital for Special Surgery Institutional Review Board (IRB# 2017-0660).

Level of Evidence

Level IV: Cross-sectional prognostic study.

Required Author Forms

Disclosure forms provided by the authors are available with the online version of this article as supplemental material.

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References

1. Agarwal S, Rosete F, Zhang C, et al. In vivo assessment of bone structure and estimated bone strength by first- and second-generation HR-pQCT. *Osteoporos Int*. 2016;27(10):2955–2966. https://doi.org/10.1007/s00198-016-3621-8
2. Braun J, Sieper J. Ankylosing spondylitis. *Lancet*. 2007;369(9570):1379–1390. https://doi.org/10.1016/S0140-6736(07)60635-7
3. Brunerová L, Ronová P, Verešová J, et al. Osteoporosis and impaired trabecular bone score in hemodialysis patients. *Kidney Blood Press Res*. 2016;41(3):345–354. https://doi.org/10.1159/000443439
4. Buie HR, Campbell GM, Klinck RJ, MacNeil JA, Boyd SK. Automatic segmentation of cortical and trabecular compartments based on a dual threshold technique for in vivo micro-CT bone analysis. *Bone*. 2007;41(4):505–515. https://doi.org/10.1016/j.bone.2007.07.007
5. Calin A, Garrett S, Whitelock H, et al. A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. *J Rheumatol*. 1994;21(12):2281–2285.
6. Caparbo VF, Furlam P, Saad CGS, et al. Assessing bone impairment in ankylosing spondylitis (AS) using the trabecular bone score (TBS) and high-resolution peripheral quantitative computed tomography (HR-pQCT). *Bone*. 2019;122:8–13. https://doi.org/10.1016/j.bone.2019.01.024
7. Peh WGC. Clinics in diagnostic imaging (70): bilateral sacroiliitis due to ankylosing spondylitis. *Singapore Med J*. 2002;43(2):107–111.
8. Creemers MCW, Franssen MJ, van't Hof MA, Gribnau FWJ, van de Putte LBA, van Riel PLCM. Assessment of outcome in ankylosing spondylitis: an extended radiographic scoring system. *Ann Rheum Dis*. 2005;64(1):127–129. https://doi.org/10.1136/ard.2004.020503
9. Deminger A, Klingberg E, Lorentzon M, et al. Factors associated with changes in volumetric bone mineral density and cortical area in men with ankylosing spondylitis: a 5-year prospective study using HRpQCT. *Osteoporos Int*. 2022;33(1):205–216. https://doi.org/10.1007/s00198-021-06049-4
10. Fonseca H, Moreira-Gonçalves D, Coriolano HJA, Duarte JA. Bone quality: the determinants of bone strength and fragility. *Sports Med*. 2014;44(1):37–53. https://doi.org/10.1007/s40279-013-0100-7
11. Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. *J Rheumatol*. 1994;21(12):2286–2291.
12. Geijer M, Gadeholt Göthlin G, Göthlin JH. The validity of the New York radiological grading criteria in diagnosing sacroiliitis by computed tomography. *Acta Radiol Stockh Swed*. 2009;50(6):664–673. https://doi.org/10.1080/02841850902914099
13. Ghozlani I, Ghazi M, Nouijai A, et al. Prevalence and risk factors of osteoporosis and vertebral fractures in patients with ankylosing spondylitis. *Bone*. 2009;44(5):772–776. https://doi.org/10.1016/j.bone.2008.12.028
14. Grazio S, Kusić Z, Cvijetić S, et al. Relationship of bone mineral density with disease activity and functional ability in patients with ankylosing spondylitis: a cross-sectional study. *Rheumatol Int*. 2012;32(9):2801–2808. https://doi.org/10.1007/s00296-011-2066-9
15. Hans D, Barthe N, Boutroy S, Pothuaud L, Winzenrieth R, Krieg MA. Correlations between trabecular bone score,

measured using anteroposterior dual-energy X-ray absorptiometry acquisition, and 3-dimensional parameters of bone microarchitecture: an experimental study on human cadaver vertebrae. *J Clin Densitom*. 2011;14(3):302–312. https://doi.org/10.1016/j.jocd.2011.05.005
16. Hoff M, Kavanaugh A, Haugeberg G. Hand bone loss in patients with psoriatic arthritis: posthoc analysis of IMPACT II data comparing infliximab and placebo. *J Rheumatol*. 2013;40(8):1344–1348. https://doi.org/10.3899/jrheum.121376
17. Jones SD, Porter J, Garrett SL, Kennedy LG, Whitelock H, Calin A. A new scoring system for the Bath Ankylosing Spondylitis Metrology Index (BASMI). *J Rheumatol*. 1995;22(8):1609.
18. Karberg K, Zochling J, Sieper J, Felsenberg D, Braun J. Bone loss is detected more frequently in patients with ankylosing spondylitis with syndesmophytes. *J Rheumatol*. 2005;32(7):1290–1298.
19. Klingberg E, Geijer M, Göthlin J, et al. Vertebral fractures in ankylosing spondylitis are associated with lower bone mineral density in both central and peripheral skeleton. *J Rheumatol*. 2012;39(10):1987–1995. https://doi.org/10.3899/jrheum.120316
20. Klingberg E, Lorentzon M, Göthlin J, et al. Bone microarchitecture in ankylosing spondylitis and the association with bone mineral density, fractures, and syndesmophytes. *Arthritis Res Ther*. 2013;15(6):R179. https://doi.org/10.1186/ar4368
21. Kohn SO, Azam A, Hamilton LE, et al. Impact of sex and gender on axSpA diagnosis and outcomes. *Best Pract Res Clin Rheumatol*. 2023;37(3):101875. https://doi.org/10.1016/j.berh.2023.101875
22. Lambert RGW, Bakker PAC, Heijde D, van der, et al. Defining active sacroiliitis on MRI for classification of axial spondyloarthritis: update by the ASAS MRI working group. *Ann Rheum Dis*. 2016;75:1958–1963. https://doi.org/10.1136/annrheumdis-2015-208642
23. Lim MJ, Kang KY. A Contemporary View of the Diagnosis of osteoporosis in patients with axial spondyloarthritis. *Front Med*. 2020;7:569449. https://doi.org/10.3389/fmed.2020.569449
24. McCloskey EV, Odén A, Harvey NC, et al. A Meta-analysis of trabecular bone score in fracture risk prediction and its relationship to FRAX. *J Bone Miner Res*. 2016;31(5):940–948. https://doi.org/10.1002/jbmr.2734
25. Muñoz-Ortego J, Vestergaard P, Rubio JB, et al. Ankylosing spondylitis is associated with an increased risk of vertebral and nonvertebral clinical fractures: a population-based cohort study. *J Bone Miner Res*. 2014;29(8):1770–1776. https://doi.org/10.1002/jbmr.2217
26. Neumann A, Haschka J, Kleyer A, et al. Cortical bone loss is an early feature of nonradiographic axial spondyloarthritis. *Arthritis Res Ther*. 2018;20(1):202. https://doi.org/10.1186/s13075-018-1620-1
27. Nigil Haroon N, Szabo E, Raboud JM, et al. Alterations of bone mineral density, bone microarchitecture and strength in patients with ankylosing spondylitis: a cross-sectional study using high-resolution peripheral quantitative computerized tomography and finite element analysis. *Arthritis Res Ther*. 2015;17:377. https://doi.org/10.1186/s13075-015-0873-1
28. Seriolo B, Paolino S, Sulli A, Ferretti V, Cutolo M. Bone metabolism changes during anti-TNF-alpha therapy in patients with active rheumatoid arthritis. *Ann N Y Acad Sci*. 2006;1069:420–427. https://doi.org/10.1196/annals.1351.040
29. Sornay-Rendu E, Cabrera-Bravo JL, Boutroy S, Munoz F, Delmas PD. Severity of vertebral fractures is associated with alterations of cortical architecture in postmenopausal women. *J Bone Miner Res*. 2009;24(4):737–743. https://doi.org/10.1359/jbmr.081223
30. Stein EM, Liu XS, Nickolas TL, et al. Microarchitectural Abnormalities are more severe in postmenopausal women with vertebral compared to nonvertebral fractures. *J Clin Endocrinol Metab*. 2012;97(10):E1918–E1926. https://doi.org/10.1210/jc.2012-1968
31. van der Heijde D, Braun J, Deodhar A, et al. Modified stoke ankylosing spondylitis spinal score as an outcome measure to assess the impact of treatment on structural progression in ankylosing spondylitis. *Rheumatol Oxf Engl*. 2019;58(3):388–400. https://doi.org/10.1093/rheumatology/key128
32. Whittier DE, Burt LA, Hanley DA, Boyd SK. Sex- and Site-Specific Reference data for bone microarchitecture in adults measured using second-generation HR-pQCT. *J Bone Miner Res*. 2020;35(11):2151–2158. https://doi.org/10.1002/jbmr.4114