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Use of Quantitative Vertebral Bone Marrow Fat Fraction to Assess Disease Activity and Chronicity in Patients with Ankylosing Spondylitis

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Objective: We quantitatively measured the fat fraction (FF) in the vertebrae of patients with ankylosing spondylitis (AS) using magnetic resonance imaging (MRI) and investigated the role of FF as an indicator of both active inflammation and chronicity.

Materials and Methods: A total of 52 patients with AS who underwent spinal MRI were retrospectively evaluated. The FF values of the anterosuperior and anteroinferior corners of the bone marrow in the L1–S1 spine were assessed using the modified Dixon technique. AS activity was measured using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), AS Disease Activity Score (ASDAS), and serum inflammatory marker levels. AS disease chronicity was assessed by AS disease duration and the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS). Univariable and multivariable regression analyses were conducted to investigate the correlation between FF and other clinical characteristics.

Results: The mean FF ± standard deviation of the total lumbar spine was 43.0% ± 11.3%. At univariable analysis, spinal FF showed significant negative correlation with BASDAI (β = -0.474, p = 0.002) and ASDAS with C-reactive protein (ASDAS-CRP; β = -0.478, p = 0.002) and a significant positive correlation with AS disease duration (β = 0.440, p = 0.001). After adjusting for patient age, sex, and total mSASSS score, spinal FF remained significantly negatively correlated with BASDAI (β = -0.543, p < 0.001), ASDAS-CRP (β = -0.568, p < 0.001), and ASDAS with erythrocyte sedimentation rate (β = -0.533, p = 0.001). Spinal FF was significantly lower in patients with very high disease activity (ASDAS-CRP > 3.5) than in those with only high disease activity (2.1 ≤ ASDAS-CRP ≤ 3.5) (p = 0.010).

Conclusion: Spinal FF may help assess both AS disease activity and chronicity.

Keywords: *Ankylosing spondylitis; Magnetic resonance imaging; Fat fraction; Disease activity; Disease chronicity*

INTRODUCTION

Ankylosing spondylitis (AS) is a common inflammatory disorder of the axial skeleton involving the sacroiliac joints and vertebrae. Enthesitis and subsequent syndesmophytes are key indicators of AS pathogenesis. Radiographic progression may occur over time, followed by inflammatory back pain [1]. AS activity is measured using patient-reported outcome measurements including pain grade, stiffness, and fatigue [2]. Disease progression is usually evaluated using conventional radiography [3].

Magnetic resonance imaging (MRI) is recommended for AS diagnosis and assessment [4]. MRI can depict the presence and amount of bone marrow edema, the hallmark of active inflammation, even in patients in early-stage AS with normal radiography findings. Furthermore, subsequent fatty degeneration, a post-inflammatory MRI finding, can be observed at the vertebral corner adherent to the inflamed

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enthesis. This vertebral corner fat deposition suggests the possibility of AS and is the strongest contributor to new bone formation and the hallmark of disease progression [5-8]. With the development of noninvasive fat quantification by chemical shift MRI, the fat fraction (FF) is now considered a substitute for invasive biopsy to investigate the distribution and quality of fat accumulation. The potential benefits of fat quantification have been reported for the detection and assessment of disorders associated with the liver, skeletal muscle, and pancreas [9-11]. This study quantitatively measured the FF in the vertebrae of patients with AS using MRI and investigated the role of FF as an indicator of both active inflammation and disease chronicity.

MATERIALS AND METHODS

Ethical Approval

This study was approved by the Institutional Review Board, which waived the requirement for informed consent due to the retrospective nature of the study (2016-04-041). This study was conducted in compliance with the Good Clinical Practice Guidelines and the principles of the Declaration of Helsinki.

Population

We retrospectively reviewed the MRI scans and medical records of 52 patients with AS who underwent MRI of the lumbar spine between March and December 2015. Patients underwent MRI to confirm the diagnosis of AS in patients with inflammatory back pain suspected of having AS or to evaluate aggravated back pain in patients with established AS. As certified by a rheumatologist, all patients fulfilled the modified New York criteria [1].

Assessment of Clinical Manifestations

Clinical characteristics including age, sex, clinical symptom duration, human leukocyte antigen (HLA)-B27 positivity, and history of uveitis and peripheral arthritis were investigated. AS disease activity was assessed using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI; 0–10) [2], AS Disease Activity Score (ASDAS)-C-reactive protein (CRP), and ASDAS-erythrocyte sedimentation rate (ESR) at the time of MRI [12]. Functional disability was assessed using the Bath Ankylosing Spondylitis Functional Index (BASFI; 0–100) [13].

The BASDAI is a validated and relevant patient-report outcome measure comprising six questions regarding fatigue, spinal pain, peripheral joint pain/swelling, enthuses symptoms, intensity of morning stiffness, and duration of morning stiffness [2]. Each question is scored based on a 10-cm visual analog scale, and the final BASDAI score ranges from 0 (no disease activity) to 10 (very active disease). A cut-off value of 4 is usually used to define active disease status. The BASFI is also a patient-reported outcome measure that evaluates the functional limitations of patients with AS. The BASFI is composed of 10 questions, with a score ranging from 0 (no functional limitation) to 10 (severe functional limitation).

The ASDAS is a composite index that includes three BASDAI questions (spinal pain, peripheral joint pain/swelling, duration of morning stiffness), as well as patient global assessment of disease activity and laboratory inflammatory markers [12]. The use of serum CRP values is recommended by the Assessment of SpondyloArthritis International Society, with ESR as a second option when CRP is not available. The relevant clinical cut-off values to differentiate disease activity states were defined according to ASDAS score in this study as follows: < 1.3 = inactive disease, ≥ 1.3–< 2.1 = moderate activity, ≥ 2.1–3.5 = high activity, and > 3.5 = very high disease activity [14].

Modified Stoke Ankylosing Spondylitis Spinal Score

Structural spinal damage was independently scored using the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) [1]. The mSASSS is the most widely used scoring method for assessing radiographic damage on conventional radiographs in patients with AS. For the mSASSS, the anterior vertebral corner of the cervical (lower border of C2 to the upper border of T1) and lumbar (lower border of T12 to the upper border of S1) vertebrae are assessed in a lateral view. The presence of bony erosion, sclerosis, or squaring (1 point), syndesmophytes (2 points), and total bony bridges (3 points) are assessed in a total of 24 vertical edges, and the total mSASSS ranges from 0–72. A two-unit change per 2 years is usually considered indicative of radiographic progression in AS [15].

Two expert radiologists blinded to the demographic and clinical data evaluated the patients' mSASSS scores. One radiologist assessed the mSASSS twice with a 7-day interval from the initial measurement; the other radiologist independently measured the mSASSS once.

Imaging Protocols for FF

Imaging was performed using a 3T MRI system (Ingenia; Philips Healthcare) with a spine matrix coil. For FF quantification, data were acquired using a 3D proton-

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density-weighted multigradient-echo sequence through receiver coil arrays. Six fractional echo magnitude images were obtained at echo times of 1.24, 2.35, 3.59, 4.83, 6.07, and 7.31 msec for T2* correction [16]. The images were processed using the two-point Dixon water/fat separation algorithm. This sequence automatically reconstructed the FF images in the sagittal plane. The following parameters were used for FF images: repetition time = 8 ms, number of excitations = 3, field of view = 285 mm, matrix size = 192 x 189 pixels, section thickness = 4 mm, intersection gap = 2 mm, flip angle = 3° (to minimize the T1-relaxation effect), and a total acquisition time of ≈ 90 seconds.

Quantification of Bone Marrow FF

Vertebral bone marrow FF was directly measured on mid-sagittal color FF maps using the modified Dixon (mDixon) technique (Fig. 1). The regions of interest (ROIs) in the anterosuperior and anteroinferior corners of the spinal bone marrow were defined on a color FF map by an expert radiologist. Post-inflammatory fat deposition on non-fat-suppressed T1 weighted images was used as a reference. Since FF can be affected by bone marrow edema, T2-weighted images were also referenced to compensate for this effect. ROI areas were approximately 50–60 mm^2, but there was no limitation to the area. We attempted to include most of the fat deposition accurately and evenly while avoiding bone cortices and syndesmophytes. The bone marrow FF of each vertebral body was calculated as $FF = S_{fat}/(S_{fat} + S_{water})$, where S_{fat} and S_{water} are the signal intensities of the fat- and water-only images, respectively [17]. The images were saved in a picture archiving and communication system (PACS; PiView STAR version 5.0, Infinitt Healthcare) at maximum magnification.

Statistical Analysis

The general statistics of the study population are

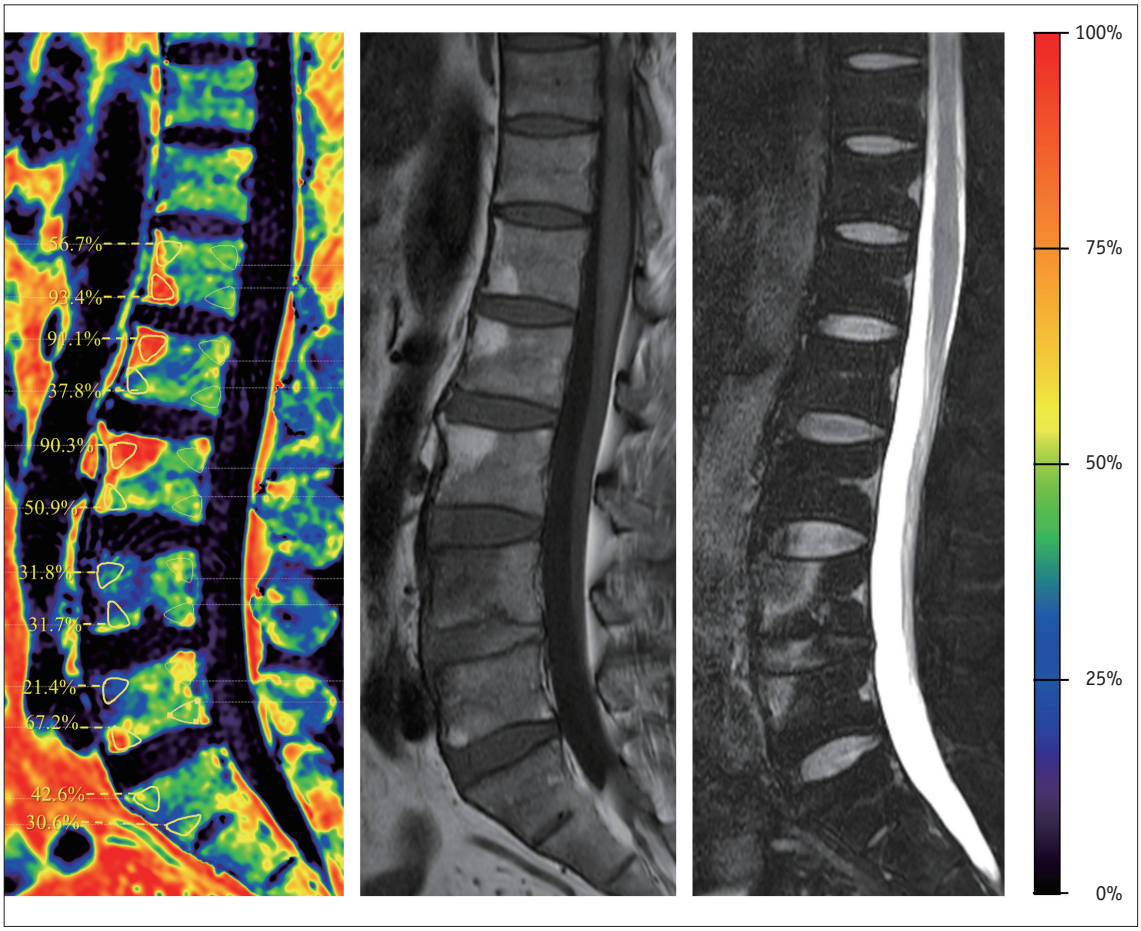

Fig. 1. Color fat fraction (%) map and non-fat suppressed T1-weighted and fat-suppressed T2-weighted sagittal magnetic resonance imaging of the L-spine. The regions of post-inflammatory fat deposition, normal marrow, and active inflammation are colored red, green or yellow, and blue, respectively. Post-inflammatory fat depositions are visible in the anterior corners of L1, L2, L3 bodies and bone marrow edema are visible in the anterosuperior corners of the L4 and L5 bodies. L = lumbar

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presented as means ± standard deviation (SD) or medians (1st interquartile, 3rd interquartile) for continuous variables and as frequencies with percentage (%) for categorical variables. The intraclass correlation coefficients (ICCs) were calculated for the total score and separately for each item using two-way mixed measures to evaluate the intra- and inter-observer agreement of the mSASSS. Univariable linear regression was used to investigate the correlation between FF and other clinical characteristics. Multivariable linear regression analysis was performed to account for age, sex, and mSASSS. Comparisons of FF between patients with high disease activity (ASDAS-CRP 2.1–3.5) and very high disease activity (ASDAS > 3.5) [14] were performed using Mann-Whitney U tests. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp.). For the regression analysis, $p < 0.005$ was considered statistically significant for a more conservative interpretation [18]. Otherwise, statistical significance was set at $p < 0.05$.

RESULTS

Demographic, Clinical, and Radiologic Characteristics

Table 1 summarizes the baseline demographic, clinical, and radiologic characteristics of the patients. A total of 52 patients underwent spinal MRI; of these, 43 (82.6%) were male. The mean patient age ± SD was 39.2 ± 13.3 years and the mean duration of AS ± SD was 61.8 ± 98.2 months. Forty-two patients (80.7%) were HLA-B27 positive. The mean BASDAI score ± SD and BASFI score ± SD were 5.2 ± 2.1 and 27.7 ± 22.7, respectively. Serum inflammatory marker levels were also elevated, with mean serum ESR ± SD and CRP level ± SD of 37.2 ± 31.4 mm/h and 2.1 ± 2.1 mg/dL, respectively.

The mean mSASSS ± SD was 18.8 ± 15.8. The intra-observer ICCs for the total mSASSS (0.99) and for the mSASSS of each vertebra (range, 0.97–0.99) were all excellent. The inter-observer ICC for the total mSASSS was also excellent (0.81; 95% confidence interval, 0.69–0.88), while the ICCs between single items were good or excellent (range, 0.66–0.94).

FF of Spinal MRI in Patients with AS

Figure 2 shows the mean and quartile FFs of spinal MRI in patients with AS. The total mean FF of the whole spine ± SD was 43.0 ± 11.3%. The mean FF values ± SD of male and female patients were 43.2 ± 11.3% and 41.8 ± 11.8%, respectively. No significant sex-based differences were observed ($p = 0.750$).

Table 1. Baseline Clinical Characteristics of Patients with AS

Variable	No. of Patients with Available Data	Value
Age at MRI, year	52	39.2 ± 13.3 (18–74)
Male	52	43 (78.2)
AS disease duration, month	52	61.8 ± 98.2 (1–456)
HLA-B27 positivity	52	42 (80.8)
ESR at MRI, mm^3/hr	51	37.2 ± 31.4 (1–122)
CRP at MRI, mg/dL	51	2.1 ± 2.1 (0.15–8.4)
BASDAI at MRI	42	5.2 ± 2.1 (0.2–9.2)
BASFI at MRI	42	2.8 ± 2.3 (0.3–9.8)
mSASSS at baseline	50	18.8 ± 15.6 (4–68)

Data presented as mean ± standard deviation (range) for continuous variables and number (%) for categorical variables. AS = ankylosing spondylitis, BASDAI = Bath Ankylosing Spondylitis Disease Activity Index, BASFI = Bath Ankylosing Spondylitis Functional Index, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, HLA = human leukocyte antigen, MRI = magnetic resonance imaging, mSASSS = modified Stoke Ankylosing Spondylitis Spinal Score

Correlation between FF and Clinical Indicators

Table 2 shows the linear regression coefficients of mean spine FF and other clinical parameters. At univariable analysis, spinal FF showed significant negative linear correlation with BASDAI (β = -0.474, $p = 0.002$), ASDAS-CRP (β = -0.478, $p = 0.002$), and ASDAS-ESR (β = -0.443, $p = 0.004$) and a significant positive linear correlation with disease chronicity, including AS disease duration (β = 0.440, $p = 0.001$).

After adjusting for patient age and sex, disease activity—including BASDAI (β = -0.499, $p = 0.001$), ASDAS-CRP (β = -0.524, $p < 0.001$), and ASDAS-ESR (β = -0.492, $p = 0.001$)—still showed significant correlation with FF. However, disease duration was not significantly correlated with spinal FF at the significance criterion of $p < 0.005$ (β = 0.333, $p = 0.017$). When adjusted for age, sex, and mSASSS, BASDAI (β = -0.543, $p < 0.001$), BASFI (β = -0.500, $p = 0.003$), ASDAS-CRP (β = -0.568, $p < 0.001$), and ASDAS-ESR (β = -0.533, $p = 0.001$) were significantly correlated with spinal FF.

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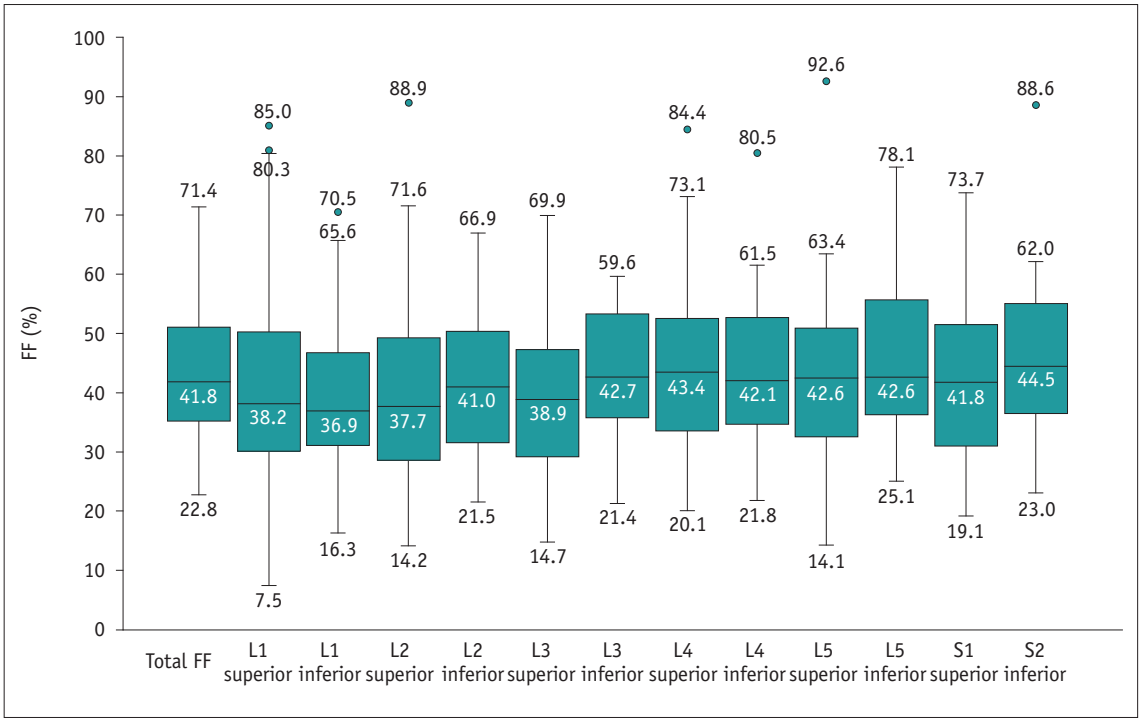

Fig. 2. Box plots representing the distribution of spinal FF (y-axis) in each vertebra (x-axis). The green box represents the interquartile range, while the solid line within the box represents the mean and the whiskers indicate 1.5 times the interquartile range. The Xs within the boxes represent the median and the green dots represent outliers. FF = fat fraction

Table 2. Linear Regression Analysis to Examine the Correlation between Fat Fractions and Clinical Indicators

	Univariable Analysis			Multivariable Analysis					
				Adjusted for Age and Sex			Adjusted for Age, Sex, and Total mSASSS		
Variable	β	B	*P**	β	B	*P**	β	B	*P**
Age, years	0.113	0.331	0.005						
Disease duration, months	0.440	0.048	0.001	0.333	0.036	0.017	0.342	0.036	0.043
ESR, mm/h	-0.093	-0.032	0.521	-0.131	-0.044	0.369	-0.216	-0.076	0.053
CRP, mg/dL	-0.218	-1.072	0.128	-0.309	-1.515	0.025	-0.354	-1.736	0.011
BASDAI	-0.474	-2.492	0.002	-0.499	-2.627	0.001	-0.543	-2.880	< 0.001
BASFI	-0.394	-0.131	0.014	-0.431	-0.143	0.005	-0.500	-0.165	0.003
ASDAS-CRP	-0.478	-5.026	0.002	-0.524	-5.518	< 0.001	-0.568	-5.965	< 0.001
ASDAS-ESR	-0.443	-4.313	0.004	-0.492	-4.792	0.001	-0.533	-5.158	0.001
mSASSS total score	0.320	0.217	0.025	0.212	0.144	0.181			

*The threshold for significance was set at $p \leq 0.005$ for a more conservative interpretation. ASDAS = Ankylosing Spondylitis Disease Activity Score, BASDAI = Bath Ankylosing Spondylitis Disease Activity Index, BASFI = Bath Ankylosing Spondylitis Functional Index, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, mSASSS = modified Stoke Ankylosing Spondylitis Spinal Score

FF Distribution by AS Disease Activity

Figure 3 shows the distribution of spinal FF according to ASDAS-CRP. In this study, 1, 2, 19, and 19 patients had low, moderate, high, and very high disease activities, respectively. The FF values (interquartile range) of patients with high and very high disease activities were 49.1% (54.5–39.5) and 38.3% (40.3–35.0), respectively. Patients with very high disease activity had lower spinal FF values than those with high disease activity ($p = 0.010$).

DISCUSSION

This study quantified spinal FF using the mDixon method and investigated its clinical significance. We discovered

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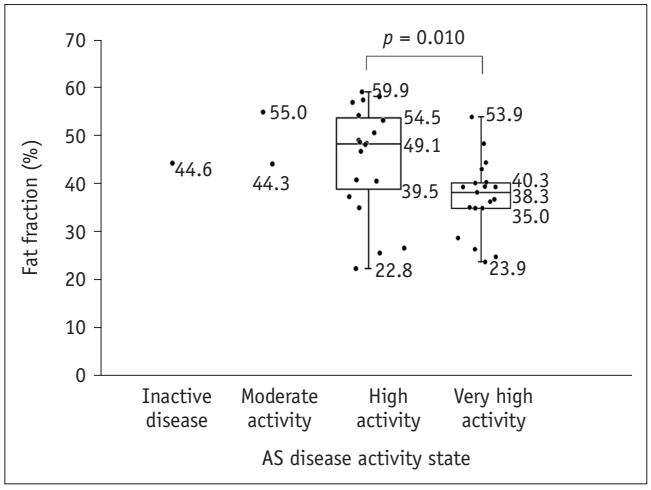

Fig. 3. Distribution of the spinal fat fraction according to disease activity. AS disease activity was measured and classified using the ASDAS based on C-reactive protein level (ASDAS score < 1.3 = inactive disease; ≥ 1.3–< 2.1 = moderate activity, ≥ 2.1–3.5 = high activity; and > 3.5 = very high disease activity). AS = ankylosing spondylitis, ASDAS = Ankylosing Spondylitis Disease Activity Score

a significant negative correlation between spinal FF and AS disease activity (BASDAI, ASDAS-CRP, and ASDAS-ESR) even after adjusting for patient age, sex, and disease chronicity score. Our results are consistent with those of a previous study that measured the sacroiliac joint FF using the mDixon method and showed that post-inflammatory FF indicated radiological chronicity in patients with spondyloarthropathy [19].

Syndesmophytes and bony ankyloses are the hallmarks of the radiographic progression of AS. These irreversible changes may decrease the range of motion and quality of life of patients with AS [20]. The bony growth occurs with local fat deposition at the same vertebral corner after inflammation caused by AS disease activity [5-7,21]. The mSASSS, which scores bony changes in the vertebral anterior corner visible on cervical and lumbar radiographs, is the most widely used measurement to assess the radiographic progression of AS [17]. However, the mSASSS is poorly standardized and the reported reliability is poor, especially among non-expert readers [22].

Previous studies have compared the presence or absence of vertebral corner fat deposition with radiographic progression, with more recent studies quantifying FF in AS patients [5,7]. We hypothesized that vertebral corner FF was associated with mSASSS, and that FF may overcome the reliability and agreement issues of mSASSS. Therefore, we investigated whether measuring the amount of fat deposition in the vertebral corner helped to define disease progression.

Noninvasive bone marrow fat quantification using MRI is also useful in other diseases. Higher bone marrow FF is associated with osteoporosis; a decrease in osteoblastogenesis in the bone marrow induces not only osteoporosis but also increased production of adipocytes with low cellularity and high fat content [23,24]. In obesity, bone marrow FF was positively associated with visceral fat, underscoring the effect of visceral fat on bone composition [25]. The prevalence of fat metaplasia in the sacroiliac joint increases with age in non-AS patients [26].

We discovered that spinal corner bone marrow FF was strongly negatively correlated with disease activity. The BASDAI is a widely used disease activity marker for AS. However, it is based on self-reported nonspecific symptoms such as the severity of inflammatory low back pain, fatigue, and quality of life [2]. While conventional laboratory inflammatory markers such as elevated CRP and ESR can provide objective information, their sensitivity and specificity are not satisfactory [27,28]. The ASDAS consists of both subjective questionnaires and objective laboratory inflammatory markers; however, both can be affected by various other medical conditions [14]. Bone marrow edema on MRI is an important finding for the diagnosis of AS in patients with back pain and the evaluation of AS disease activity. Recent guidelines recommend sacral joint and spinal MRI for the diagnosis of axial vertebral joint disease [29].

The FF was calculated by dividing the signal intensity fat-only image by the sum of the fat-only and water-only image signal intensities, $S_{fat}/(S_{fat} + S_{water})$. According to the calculation formula, the FF was inversely correlated with the fraction (amount) of water (bone marrow edema); in this study, FF showed a strong negative correlation with BASDAI score. Therefore, FF may reflect both the degree of inflammation quantified by imaging and the AS disease activity evaluated by the patient's symptoms. Recent studies have also investigated the usefulness of apparent diffusion coefficient (ADC) values from diffusion-weighted MRI films of the sacroiliac joint for distinguishing axial spondyloarthropathy from other non-inflammatory diseases with back pain, as ADC values are influenced by tissue water content [30,31].

Several studies have compared MRI scores, such as the Berlin MRI Score and the Spondyloarthritis Research Consortium of Canada Score in patients with AS activity or pain. However, these scoring systems are manual semiquantitative systems that measure the amount of bone

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marrow edema by assigning point values of 0 to 3. Some studies have failed to demonstrate a significant correlation of any score with the pain score, BASDAI, ASDAS-CRP, and ASDAS-ESR [30,32-35]. A recent study quantified the amount of water using ADC values and showed good performance in discriminating axial spondyloarthropathy from other diseases. However, they found no correlation between ADC values and BASDAI, ASDAS-CRP, or ASDAS-ESR. The authors speculated that the limited ADC resolution made it difficult to localize the active lesions on MRI; thus, the ADC measurement "precludes evaluation of patients with predominant active spinal disease" [30]. Unlike these conventional semiquantitative scoring systems, FF calculation using the mDixon method showed a significant negative correlation with AS disease activity. Therefore, the complementary use of the FF in existing MRI scoring systems, such as Berlin MRI scores or ADC values, can provide additional quantitative and objective information about AS disease activity.

We propose the use of the mDixon method as a useful tool for assessing disease activity in patients with AS. Although UK guidelines suggest that short tau inversion recovery (STIR) images are sufficient to detect inflammation, other guidelines still recommend the use of T1-gadolinium imaging to detect inflammatory lesions [29,36]. The mDixon method requires a shorter examination time and lower signal-to-noise ratio. Thus, it is more effective at suppressing fat signals than conventional STIR images and may help to avoid the potential adverse effects of gadolinium exposure.

This study had several limitations. First, the analysis did not include bone mineral density, an important factor affecting FF. However, the impact of osteoporosis is likely negligible because most of our patients were young (mean age 39 years) and men (78.2%). Second, this study was cross-sectional in design. Follow-up FF data may show disease progression in more detail. Third, most patients were in an active state and the number of inactive patients was insufficient. However, MRI was performed in patients with pain and our study was based on real-world data; therefore, it would be natural that most patients had high disease activity. Another limitation was the lack of a normal control group.

In conclusion, quantitative measurement of the amount of fat infiltration in the L1–S1 spinal bone marrow of patients with AS by FF using the mDixon method may be correlated with disease activity and chronicity. Thus, FF may help to assess the disease status of patients with AS.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Bon San Koo, Seunghun Lee. Data curation: Seunghun Lee, Tae-Hwan Kim. Formal analysis: Ga Young Ahn, Bon San Koo. Investigation: Kyung Bi Joo, Seunghun Lee. Methodology: Ga Young Ahn, Bon San Koo. Project administration: Tae-Hwan Kim, Seunghun Lee. Resources: Seunghun Lee. Software: Seunghun Lee. Supervision: Tae-Hwan Kim, Seunghun Lee. Visualization: Ga Young Ahn, Seunghun Lee. Writing—original draft: Ga Young Ahn, Bon San Koo. Writing—review & editing: all authors.

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