

ORIGINAL ARTICLE

Fat metaplasia on MRI of the sacroiliac joints increases the propensity for disease progression in the spine of patients with spondyloarthritis

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ABSTRACT

Objective: We tested the hypothesis that fat metaplasia on MRI of the sacroiliac joints (SIJ) increases the propensity for new bone formation in the spine of patients with spondyloarthritis.

Methods: We assessed baseline T1-weighted and short τ inversion recovery SIJ MRIs from patients in the Follow Up Research Cohort in Ankylosing Spondylitis (FORCAST). Radiographic progression was assessed using the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS). Structural and inflammatory lesions were scored using the Spondyloarthritis Research Consortium of Canada (SPARCC) SIJ structural and SPARCC SIJ inflammation scores, respectively. Radiographic progression was compared in cases with and without definite MRI lesions (score ≥ 2 or < 2) and the extent of MRI lesions at baseline was compared in patients with and without radiographic progression. The predictive capacity of MRI SIJ lesions for radiographic progression in the spine was assessed in univariate and multivariate regression analyses.

Results: The extent of MRI structural lesions in the SIJ at baseline was significantly greater in those patients who had spinal radiographic progression on follow-up ($p=0.003$, 0.02 , 0.003 for fat metaplasia, backfill and ankylosis, respectively). Also, radiographic progression was significantly greater in cases with definite baseline SIJ ankylosis ($p=0.008$). In multivariate regression that included all types of MRI lesions and was adjusted for age, sex, symptom duration, duration of follow-up, CRP, baseline mSASSS and treatment, the extent of SIJ fat metaplasia and ankylosis at baseline were independently associated with radiographic progression.

Conclusions: SIJ ankylosis and fat metaplasia but not inflammatory lesions increase the propensity for radiographic progression in the spine.

INTRODUCTION

Spondyloarthritis (SpA) is an inflammatory disorder of the axial spine that typically begins with inflammation in the sacroiliac

Key messages

What is already known about this subject?

- Relatively little is known regarding predictors of radiographic progression in the spine of patients with spondyloarthritis.

What does this study add?

- This prospective cohort study demonstrates that structural lesions rather than inflammation on MRI of the sacroiliac joints (SIJ) are predictive of radiographic progression in the spine.
- The reparative response to inflammation as manifest by the appearance of fat metaplasia on the T1-weighted MRI of the SIJ predicts new bone formation in the spine.

How might this impact on clinical practice?

- The early appearance of fat metaplasia on MRI of the SIJ may help identify a phenotype of patient at increased risk of disease progression to the spine and requiring more intensive therapy.

joints (SIJ). MRI constitutes a major advance over radiography through its ability to demonstrate active inflammation on fat-suppressed sequences such as short τ inversion recovery (STIR). Several studies have now demonstrated that resolution of inflammation is associated with the development of fat metaplasia on T1-weighted (T1W) sequences and that this may be an important intermediary tissue along the pathway to new bone formation in the SIJ and spine.^{1–3}

Recent MRI data have shown that resolution of bone marrow edema (BME) at vertebral corners is associated with the development of fat metaplasia and later also development of new syndesmophytes at the same location.^{4–6} In the SIJ, we have previously shown that resolution of inflammatory

lesions at the site of erosions is followed by development of a new tissue that also has high signal intensity on T1W MRI.^{2,3} We have called this type of lesion ‘backfill’ due to its appearance in the excavated area caused by erosion.⁷ We also demonstrated that backfill and fat metaplasia are associated with the development of SIJ ankylosis independently of other potential predictors.³

These observations can be interpreted as indicating that the appearance of fat metaplasia reflects a disease phenotype associated with an increased propensity for local new bone formation. This hypothesis could further predict that the development of fat metaplasia in the SIJ precedes new bone formation in the SIJ and in the spine. Spinal ankylosis is of major significance because it is the primary factor associated with functional impairment, but it also represents a late feature of the disease. There are relatively few prognostic indicators for spinal ankylosis once analysis is adjusted for baseline severity of radiographic changes as measured using the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS).^{8–10} There is a major unmet need for lead indicators of radiographic progression in the spine to help select at-risk patients to participate in trials of disease-modifying therapies and for early intervention strategies in SpA. Consequently, we aimed to test the hypothesis that MRI structural lesions in the SIJ, especially fat metaplasia and ankylosis, may predict new bone formation on spinal radiographs from patients with axial SpA and thereby address a key preliminary requirement in the validation of a surrogate imaging biomarker for radiographic progression in the spine of patients with SpA.

METHODS

Patients

We assessed all available baseline SIJ MRIs (n=232) from 431 patients with SpA according to the modified New York criteria¹¹ consecutively recruited to the Follow Up Research Cohort in Ankylosing Spondylitis (FORCAST) who had available baseline and follow-up lumbar and cervical radiographs that had been conducted at least 2 years after the baseline visit. We compared those with and without available MRIs to examine evidence for selection bias according to baseline characteristics and radiographic progression. Patients in the study attended systematic clinical and laboratory evaluation according to a standardised protocol every 6 months for the first 3 years and thereafter annually.³ The study received ethical approval from the Health Research Ethics Board of the University of Alberta and was performed in accordance with the Helsinki Declaration. Written informed consent was obtained from all study participants before inclusion into the observational cohort.

Radiographic reading, calibration and reliability exercise

Lateral radiographs of the cervical and lumbar spine were independently evaluated by two readers and an

adjudicator blinded to patient demographics, MRI and treatment. Baseline and first follow-up radiographs for each case were read and scored in pairs using the mSASSS.¹² Adjudication by a third reader was prespecified when the discrepancy between the two primary readers in the change in mSASSS was ≥ 5 and then the mean of the adjudicator’s score and the closest score of the two primary readers was considered the final score. Two pivotal clinical trials of tumour necrosis factor (TNF) inhibitors (TNFis) in ankylosing spondylitis (AS), one evaluating infliximab in the ASSERT trial¹³ and the second assessing adalimumab in the ATLAS trial,¹⁴ used adjudication for assessment of radiographic progression for reader discrepancy of ≥ 5 mSASSS units in 2-year change scores. Consequently, we adopted this same approach of using adjudication when reader discrepancy in 2-year change score was ≥ 5 mSASSS units. Calibration of readers was undertaken using the Spondyloarthritis Radiography Reference (SPAR) module, which is a validated calibration tool.¹⁵ Thereafter, a reliability exercise was conducted on baseline and 2-year pairs of radiographs from 84 cases that were assessed blinded to time point. The interobserver intraclass correlation coefficient (ICC) for the two primary readers was 0.98 for status scores at baseline and 0.79 for change scores. For the entire reading exercise of 431 patients, adjudication was necessary in 46 (10.6%) cases. Readers also specifically recorded the presence of new syndesmophytes on the follow-up radiograph.

MRI protocol

The SpA MRI protocol has been reported previously.³ Scans were semicoronal T1-weighted turbo spin-echo (T1WSE) sequences of the SIJ. The scan parameters were as follows: 15–19 slices, 4 mm slice thickness, 0.4 mm interslice gap, field of view 280–300 mm, repetition time 423–450 ms, echo time 12–13 ms, echo train length 3 and matrix 512×256 pixels.

MRI SIJ lesion scoring methodology, calibration and reading exercises

Inflammatory lesions in the SIJ were assessed on STIR scans by two readers using the Spondyloarthritis Research Consortium of Canada (SPARCC) MRI method.¹⁶ MRI structural lesions in the SIJ were assessed on T1WSE scans using the SPARCC MRI SIJ Structural Scoring (SSS) method.¹⁷ Structural lesions were assessed independently of MRI inflammation by a different primary reader pair as recommended in the SSS method to avoid bias from interpretation of BME on STIR scans where a considerable proportion of patients receive TNFi therapy. We adopted standardised definitions of structural lesions of the SIJ on MRI for fat metaplasia, erosion and ankylosis, which were developed by the Canada–Denmark MRI Working Group,¹⁸ and which were extended in a subsequent report to include backfill.⁷ Calibration of readers was undertaken using a validated calibration tool available at <http://www.carearthritis>.

com/mriportal/sss/index/ and a preliminary exercise was conducted on 66 T1W MRIs to assess reader reliability (ICC (95% CIs), which was as follows: fat metaplasia: 0.72 (0.55 to 0.83); erosion: 0.77 (0.65 to 0.85); backfill: 0.66 (0.49 to 0.79); ankylosis: 0.95 (0.91 to 0.98)).

Statistics

Radiographic progression was defined as a linear rate variable, reflecting the mean mSASSS unit progression per year, and also as a dichotomous variable, indicating the presence/absence of any progression (>0 mSASSS units/year). Lack of development of new bone was prespecified as lack of occurrence of structural changes such as syndesmophytes or ankylosis in any anterior vertebral corner on lateral radiographs of the cervical and lumbar spine after ≥ 10 years from onset of symptoms and for the entire duration of prospective follow-up. Radiographic progression was also defined according to the development of a new syndesmophyte (yes/no).

MRI scores for SIJ lesions were calculated according to the mean of the reader scores. We also defined an MRI lesion as being definitely present in the SIJ when there was

a score of ≥ 2 for that specific lesion as recorded by *both* readers.

We used the t-test, Mann-Whitney U test and Fisher's exact test as appropriate to compare demographic variables, clinical characteristics and MRI SIJ lesion scores in patients with and without radiographic progression. Radiographic progression in patients with and without a definite MRI SIJ lesion was also compared using the same group statistics.

We used univariate regression analyses to identify demographic, clinical, and baseline radiographic and MRI lesion parameters associated with radiographic progression. Significant variables from univariate analyses were included in a primary regression model for multivariate analyses. The core variable group for this regression model included age, sex, symptom duration, baseline CRP, baseline mSASSS, duration of follow-up and treatment. MRI SIJ structural lesions were added, individually and simultaneously, to the primary regression model to determine which lesions were independently associated with spinal progression. Multivariate analyses were conducted using linear regression where the dependent variable was the change in mSASSS, and

Table 1 Baseline demographic characteristics, clinical and imaging variables in the FORCAST study population with radiographic progression data for the spine over at least 2 years

	All patients (N=431)	Available MRI (N=232)	No available MRI (N=199)	p Value
Age (mean (SD))	42.4 (12.5)	40.8 (11.9)	44.2 (12.9)	0.01
Males (N (%))	318 (73.8%)	169 (72.8%)	149 (74.9%)	0.67
Symptom duration (mean (SD) years)	18.3 (11.5)	17.1 (10.8)	19.8 (12.3)	0.04
Smokers*				
Current, N (%)	74 (21.1%)	37 (19.6%)	37 (23%)	0.51
Pack years smoked (mean (SD))	6.5 (9.4)	5.4 (8.7)	7.8 (10.1)	0.01
N (%) smoked >10 pack years	85 (25.7%)	39 (22.0%)	46 (29.9%)	0.13
BASDAI (mean (SD))	5.1 (2.4)	5.1 (2.4)	5.2 (2.5)	0.47
ASDAS (mean (SD))	3.8 (1.4)	3.8 (1.4)	3.8 (1.5)	0.95
CRP (mean (SD) mg/L)	14.5 (20.1)	12.4 (16.4)	17 (23.5)	0.16
N (%) HLA-B27 positive†	325 (84%)	175 (84.1%)	150 (83.8%)	1.0
N (%) on NSAIDs	347 (80.5%)	188 (81%)	159 (79.9%)	0.81
N (%) on TNF- α inhibitor	266 (61.7%)	134 (57.8%)	132 (66.3%)	0.07
mSASSS (mean (SD))	17.1 (20.6)	13.7 (18.1)	21.2 (22.6)	0.0002
Duration of follow-up (mean (SD)) (range) months	31.9 (13.6) (18–105)	30.9 (12.6) (18–105)	33.1 (14.6) (18–98)	0.22
Δ mSASSS (mean (SD))	2.3 (3.8)	2.4 (4.3)	2.2 (3.2)	0.69
Δ mSASSS progression rate (mean (SD)) mSASSS units/year	0.83 (1.3)	0.85 (1.3)	0.81 (1.2)	0.65
N (%) with no progression over ≥ 2 years	204 (47.3%)	105 (45.3%)	99 (49.7%)	0.38
N (%) with average Δ mSASSS progression rate >0 units/year	227 (52.7%)	127 (54.7%)	100 (50.3%)	0.38
N (%) with average Δ mSASSS progression rate ≥ 1 unit/year for ≥ 2 years	136 (31.6%)	76 (32.8%)	60 (30.2%)	0.67
N (%) with new syndesmophyte‡	49 (23.7%)	30 (23.3%)	19 (24.4%)	0.87

*Data from 350 patients (331 with pack years data).

†Data from 387 patients.

‡Patients with 2-year follow-up (± 2 -month window; n=207).

ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C-reactive protein; FORCAST, Follow Up Research Cohort in Ankylosing Spondylitis; HLA, human-leucocyte-antigen; mSASSS, modified Stoke Ankylosing Spondylitis Spine Score; NSAID, non-steroidal anti-inflammatory drug; TNF, tumour necrosis factor.

Table 2 Baseline demographic, clinical and imaging variables in the FORCAST study population according to the presence or absence of radiographic progression in the spine

	Δ mSASSS progression rate=0 over ≥ 2 years N=204	Δ mSASSS progression rate >0 N=227	p Value
Age (mean (SD))	39.8 (13.0)	44.7 (11.5)	<0.0001
Males (N (%))	142 (69.6%)	176 (77.5%)	0.06
Symptom duration (mean (SD) years)	16.2 (11.3)	20.2 (11.4)	<0.001
Duration of follow-up (mean (SD) (range) years)	2.4 (1.0) (1.5–8.2)	2.9 (1.3) (1.5–8.8)	<0.001
Smokers*			
Current, N (%)	37 (22.3%)	37 (20.1%)	0.69
Pack years smoked (mean (SD))	6.3 (9.4)	6.7 (9.5)	0.94
N (%) smoked >10 pack years†	38 (23.8%)	47 (27.5%)	0.45
BASDAI (mean (SD))	5.1 (2.5)	5.2 (2.4)	0.89
ASDAS (mean (SD))	3.7 (1.5)	3.9 (1.4)	0.12
CRP (mean (SD) mg/L)	13.2 (19.7)	15.6 (20.4)	0.08
N (%) HLA-B27 positive‡	151 (84.8%)	174 (83.3%)	0.78
N (%) on NSAIDs	162 (79.4%)	185 (81.5%)	0.63
N (%) on TNF- α inhibitor	127 (62.3%)	139 (61.2%)	0.84
mSASSS (mean (SD))	14.5 (22.7)	19.5 (18.3)	<0.0001
SPARCC SIJ inflammation (mean (SD))§	8.1 (9.8)	6.9 (10.0)	0.28
N (%) with SPARCC SIJ ≥ 2 §	48 (45.7%)	55 (44.4%)	0.79
SSS fat metaplasia (mean (SD))¶	2.5 (4.2)	5.2 (7.0)	0.003
N (%) with SSS fat metaplasia ≥ 2 ¶	29 (27.6%)	49 (38.6%)	0.09
SSS erosion (mean (SD))¶	3.8 (4.2)	2.4 (3.7)	0.007
N (%) with SSS erosion ≥ 2 ¶	40 (38.1%)	33 (26.6%)	0.06
SSS backfill (mean (SD))¶	2.2 (3.3)	3.5 (4.3)	0.02
N (%) with SSS backfill ≥ 2 ¶	22 (21%)	36 (28.3%)	0.22
SSS ankylosis (mean (SD))¶	4.1 (7.2)	6.3 (7.9)	0.003
N (%) with SSS ankylosis ≥ 2 ¶	27 (25.7%)	55 (43.3%)	0.006

*Data from 350 patients.

†Data from 331 patients.

‡Data from 387 patients.

§Data from 229 patients.

¶Data on 232 patients.

ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C-reactive protein; FORCAST, Follow Up Research Cohort in Ankylosing Spondylitis; HLA, human-leucocyte-antigen; mSASSS, modified Stoke Ankylosing Spondylitis Spine Score; NSAID, non-steroidal anti-inflammatory drug; SIJ, sacroiliac joints; SPARCC, Spondyloarthritis Research Consortium of Canada; SSS, SPARCC MRI SIJ Structural Scoring; TNF, tumour necrosis factor.

using logistic regression where the dependent variable was the development of a new syndesmophyte (yes/no). In additional univariate and multivariate conditional logistic regression analyses, we used data from patients matched for age, symptom duration and duration of follow-up, to determine which demographic, clinical and imaging variables were independently associated with the absence of syndesmophytes and ankylosis at anterior vertebral corners on cervical and lumbar radiographs.

RESULTS

Baseline characteristics and radiographic follow-up

The baseline demographic and disease status characteristics of the study population were typical of SpA cohorts with a preponderance of males (73.1%) and 84% who were human-leucocyte-antigen (HLA)-B27 positive

(table 1). Most patients (76.7%) had definite structural lesions in the SIJ on MRI at baseline, as defined by an SSS score of ≥ 2 recorded by both readers in at least one scoring domain (erosion (31.5%), fat metaplasia (33.6%), backfill (25.0%), ankylosis (35.3%)). Patients were followed for a mean (SD) of 31.4 (13.7) months and a slight majority of patients (52.4%) had evidence of spinal radiographic progression after follow-up. Patients without available MRIs at the start of the radiographic follow-up were significantly older with longer symptom duration and more severe radiographic changes but otherwise had similar baseline characteristics and spinal radiographic progression on follow-up as those patients with available baseline scans (table 1). There were 61 (14.2%) patients who had no syndesmophytes or ankylosis on cervical and lumbar spine radiographs after ≥ 10 years from onset of symptoms and for the entire duration of prospective follow-up.

Table 3 Clinical, laboratory and imaging parameters at baseline in FORCAST patients matched for age, symptom duration and follow-up duration according to the presence (damage) or absence (lack of damage) of any syndesmophytes or ankylosis on cervical and lumbar spine radiographs*

	Damage (n=81)	Lack of damage (n=42)	p Value
Age (mean (SD))	41.80 (8.64)	39.48 (9.03)	0.13
Males (N (%))	66 (82.5%)	24 (57.0%)	0.004
Smoking pack years (mean (SD))	6.92 (9.49)	5.69 (9.12)	0.94
Current smoker (N (%))	15 (23.4%)	8 (25.0%)	1.000
Pack years >10 (N (%))	21 (33.9%)	5 (16.1%)	0.089
TNFi treated (N (%))	50 (62.5%)	23 (54.8%)	0.44
NSAID treated (N (%))	65 (81.2%)	33 (78.6%)	0.81
HLA-B27 positive (N (%))	58 (81.7%)	29 (76.3%)	0.617
BASDAI (mean (SD))	5.38 (2.49)	5.09 (2.52)	0.44
ASDAS (mean (SD))	4.00 (1.34)	3.44 (1.56)	0.061
CRP (mean (SD))	14.32 (15.89)	9.22 (10.74)	0.02
SPARCC SIJ inflammation (mean (SD))	6.04 (9.03)	7.54 (8.46)	0.22
SPARCC SIJ>2 (N (%))	16 (35.6%)	15 (55.6%)	0.14
SSS fat metaplasia (mean (SD))	4.69 (6.23)	1.91 (3.44)	0.029
SSS fat metaplasia ≥ 2 (N (%))	18 (40.0%)	6 (20.7%)	0.13
SSS erosion (mean (SD))	2.69 (3.98)	4.16 (3.74)	0.019
SSS erosion ≥ 2 (N (%))	14 (31.1%)	14 (48.3%)	0.15
SSS backfill (mean (SD))	4.22 (4.92)	1.76 (2.25)	0.051
SSS backfill ≥ 2 (N (%))	13 (28.9%)	5 (17.2%)	0.28
SSS ankylosis (mean (SD))	8.98 (8.92)	2.41 (4.60)	0.003
SSS ankylosis >2 (N (%))	24 (53.3%)	6 (20.7%)	0.007

*Mean (SD) duration of symptoms and prospective follow-up was 18.0 (7.0) and 2.3 (0.49) years in those cases lacking damage and 17.5 (8.2) and 2.6 (1.4) years in those with damage.

ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C-reactive protein; FORCAST, Follow Up Research Cohort in Ankylosing Spondylitis; HLA, human-leucocyte-antigen; NSAID, non-steroidal anti-inflammatory drug; SPARCC, Spondyloarthritis Research Consortium of Canada; SSS, SPARCC MRI SIJ Structural Scoring; TNFi, tumour necrosis factor inhibitor.

MRI structural lesions according to presence/absence of radiographic progression in the spine

Patients with radiographic progression in the spine ($\Delta mSASSS > 0$) were older, more likely to be male, had longer symptom duration, higher AS Disease Activity Score (ASDAS) and CRP, and significantly more radiographic damage in the spine at baseline (table 2). MRI SSS scores for SIJ fat metaplasia ($p=0.003$), backfill ($p=0.02$) and ankylosis ($p=0.003$) were significantly higher in progressors while SSS score for erosion was significantly lower ($p=0.007$). No significant differences were observed in the level of current or past smoking, level of SIJ inflammation on MRI, or prevalence of HLA-B27 between progressors and non-progressors.

Patients who had no syndesmophytes or ankylosis on cervical and lumbar spine radiographs after ≥ 10 years from onset of symptoms and following the entire duration of prospective follow-up ($n=42$) were matched for age, symptom duration and duration of follow-up with patients who had developed syndesmophytes or ankylosis by the end of the follow-up ($n=81$; table 3). The group lacking damage had significantly fewer males ($p=0.004$), lower CRP ($p=0.02$) and lower MRI SIJ scores for fat ($p=0.03$) and ankylosis ($p=0.003$) while the score for SIJ erosion was significantly higher ($p=0.02$). Definite SIJ ankylosis (SSS score ≥ 2 by both

readers) was evident in 20.7% of cases in those cases lacking damage versus 53.3% of those with damage ($p=0.007$).

Spinal radiographic progression according to presence/absence of definite MRI SIJ structural lesions

The rate of radiographic progression was significantly greater in patients with definite SIJ ankylosis ($p=0.008$), and lower in those with definite SIJ erosion ($p=0.014$; table 4). This was also observed when only patients who received TNF- α therapy during follow-up were analysed. When only patients who received standard therapy (non-steroidal anti-inflammatory agents and/or physiotherapy) during follow-up were analysed, the rate of radiographic progression was significantly greater only in patients with definite fat metaplasia ($p=0.026$).

Univariate analyses

Univariate regression analyses identified older age, longer symptom duration, male sex, and level of ASDAS and CRP as being significantly associated with a higher rate of radiographic progression (table 5). HLA-B27, smoking, treatment and SIJ inflammation on MRI were not significant factors. Among baseline imaging parameters, higher mSASSS, higher SSS scores for fat metaplasia, backfill and ankylosis, and lower SSS score for

Table 4 Radiographic progression in the spine in the FORCAST study population according to the presence/absence of definite MRI lesions in the sacroiliac joints at baseline

	SPARCC SIJ $\geq 2^*$		SSS fat metaplasia ≥ 2		SSS erosion ≥ 2		SSS backfill ≥ 2		SSS ankylosis ≥ 2	
	Yes N=103	No N=126	Yes N=78	No N=154	Yes N=73	No N=159	Yes N=58	No N=174	Yes N=82	No N=150
All patients										
Δ mSASSS units/year (mean (SD))	0.74 (1.11)	0.94 (1.50)	1.09 (1.51)	0.73 (1.23)	0.56 (1.01)	0.98 (1.44)	0.89 (1.19)	0.84 (1.38)	1.12 (1.63)	0.70 (1.12)
Patients on standard therapy (N=98)										
Δ mSASSS units/year (mean (SD))	0.76 (1.26)	0.77 (1.08)	1.24 (1.56)	0.57 (0.86)	0.53 (0.82)	0.89 (1.27)	1.15 (1.47)	0.67 (1.04)	0.93 (1.18)	0.72 (1.14)
Patients on TNFi therapy (N=134)										
Δ mSASSS units/year (mean (SD))	0.73 (0.99)	1.06 (1.73)	0.99 (1.48)	0.86 (1.45)	0.59 (1.15)	1.05 (1.56)	0.75 (0.99)	0.96 (1.60)	1.22 (1.81)	0.69 (1.11)

* Available SPARCC SIJ scores n=229. FORCAST, Follow Up Research Cohort in Ankylosing Spondylitis; SPARCC, Spondyloarthritis Research Consortium of Canada; SSS, SPARCC MRI SIJ Structural Scoring; TNFi, tumour necrosis factor inhibitor.

Table 5 Univariate linear regression analysis to identify demographic, clinical and imaging parameters associated with the degree of radiographic progression in the spine in the FORCAST cohort of patients with SpA

Variable	β ratio	SE	p Value
Age	0.010	0.003	0.0002
Sex	-0.15	0.074	0.05
Symptom duration	0.010	0.003	0.0006
Duration of follow-up	0.005	0.0024	0.04
Current smoker (Y/N)	-0.053	0.089	0.56
Pack years	0.002	0.004	0.70
>10 Pack years (Y/N)	0.068	0.085	0.43
ASDAS	0.056	0.024	0.020
CRP	0.004	0.0017	0.021
HLA-B27	-0.037	0.095	0.70
Treatment TNFi (Y/N)	0.024	0.067	0.72
NSAID (Y/N)	0.080	0.083	0.33
Baseline mSASSS	0.005	0.002	0.001
SPARCC SIJ score	-0.006	0.005	0.19
SPARCC SIJ ≥ 2 (Y/N)	-0.08	0.091	0.34
SSS erosion score	-0.033	0.011	0.003
SSS erosion ≥ 2 (Y/N)	-0.013	0.053	0.80
SSS fat metaplasia score	0.031	0.007	<0.0001
SSS fat metaplasia ≥ 2 (Y/N)	0.20	0.094	0.04
SSS backfill score	0.025	0.011	0.03
SSS backfill ≥ 2 (Y/N)	0.084	0.103	0.42
SSS ankylosis score	0.015	0.006	0.009
SSS ankylosis ≥ 2 (Y/N)	0.26	0.092	0.006

ASDAS, Ankylosing Spondylitis Disease Activity Score; CRP, C-reactive protein; FORCAST, Follow Up Research Cohort in Ankylosing Spondylitis; HLA, human-leucocyte-antigen; mSASSS, modified Stoke Ankylosing Spondylitis Spine Score; N, no; NSAID, non-steroidal anti-inflammatory drug; SpA, spondyloarthritis; SPARCC, Spondyloarthritis Research Consortium of Canada; SSS, SPARCC MRI SIJ Structural Scoring; TNFi, tumour necrosis factor inhibitor; Y, yes.

erosion were associated with a higher rate of radiographic progression. In addition, the presence of definite (SSS score ≥ 2) fat metaplasia or ankylosis was associated with radiographic progression.

Multivariate analyses

Clinical and laboratory variables significantly associated with radiographic progression in univariate analyses were included together with treatment as a core group of variables in the primary regression model (table 6). These core variables included age, sex, symptom duration, baseline CRP, baseline mSASSS, duration of follow-up and treatment. When each MRI lesion was individually added to the primary regression model containing all the core variables, only SSS score for fat metaplasia was independently associated with radiographic progression as measured by the mSASSS (β coefficient=0.027, $p < 0.001$). When all MRI lesion scores were simultaneously added to the primary regression model containing all the core variables, fat metaplasia and ankylosis were both independently associated with radiographic progression (SSS fat: β coefficient=0.025, $p < 0.001$; SSS ankylosis: β coefficient=0.012, $p = 0.047$).

Table 6 Multivariate stepwise linear regression analysis of clinical and imaging variables associated with the degree of radiographic progression in the spine as measured by the mSASSS in the FORCAST cohort of patients with SpA

Regression model	Adjusted R ²	Significant variables	β coefficient	p Value
Primary model (age, sex, symptom duration, duration of follow-up, BL CRP, BL mSASSS, treatment)	0.054	Age	0.011	<0.001
		Duration of follow-up	0.004	0.03
		CRP	0.005	0.03
Primary model plus SSS fat metaplasia score	0.14	Age	0.011	0.002
		Duration of follow-up	0.010	0.002
		Fat metaplasia	0.027	<0.001
Primary model plus SSS erosion score	0.10	Age	0.015	<0.001
		CRP	0.006	0.02
		Duration of follow-up	0.011	0.002
Primary model plus SSS backfill score	0.10	Age	0.015	<0.001
		CRP	0.006	0.016
		Duration of follow-up	0.011	0.002
Primary model plus SSS ankylosis score	0.10	Age	0.015	<0.001
		CRP	0.006	0.018
		Duration of follow-up	0.011	0.002
Primary model plus SSS fat metaplasia, erosion, backfill, ankylosis scores	0.15	Age	0.010	0.01
		Duration of follow-up	0.011	0.001
		Fat metaplasia	0.025	0.001
		Ankylosis	0.012	0.047

BL CRP, Basile C-reactive protein; FORCAST, Follow Up Research Cohort in Ankylosing Spondylitis; mSASSS, modified Stoke Ankylosing Spondylitis Spine Score; SpA, spondyloarthritis; SPARCC, Spondyloarthritis Research Consortium of Canada; SSS, SPARCC MRI SIJ Structural Scoring.

When the presence/absence of definite (SSS score ≥ 2 by both readers) MRI structural lesions was included with the core variable group in the multivariate linear regression analysis, only definite ankylosis was independently associated with radiographic progression (β coefficient=0.20, $p=0.038$).

In the logistic regression model, where development of new syndesmophyte was the dependent variable, SSS score for ankylosis was the only independent predictor when absolute scores for all structural lesions were entered into the model (OR (95% CI)=1.05 (1.01 to 1.09), $p=0.02$). When the presence/absence of all definite (SSS score ≥ 2 by both readers) MRI structural lesions was included with the core variable group in the multivariate logistic regression analysis, only definite ankylosis was independently associated with radiographic progression (OR (95% CI)=2.40 (1.26 to 4.55 to 1.09), $p=0.008$; see online supplementary table).

We conducted additional multivariate analyses to address collinearity between age and disease duration and retained only age in the models. Results for linear regression analysis of mSASSS progression were mostly similar to the model that included both age and disease duration (table 6), the primary difference being that only SIJ fat metaplasia (SSS fat score) was independently associated with mSASSS progression (SSS fat: β coefficient=0.027, $p<0.001$) when all MRI lesion SSS scores were simultaneously added to the primary regression model containing all the core variables. Results for logistic regression analysis of development of new syndesmophytes did not show any difference from the model that

included both age and disease duration in demonstrating CRP and MRI SIJ ankylosis as predictors of new syndesmophytes.

We added the interaction terms smoking/SSS fat score or TNF treatment/SSS fat score into models that also included a smoking variable (current smoking (yes/no) or number of pack years), SSS score for fat and the core variables used in all the multivariate analyses: age, sex, symptom duration, baseline CRP, baseline mSASSS, duration of follow-up and treatment. Neither smoking nor treatment was an effect modifier in the predictive association of SIJ fat metaplasia for mSASSS progression.

DISCUSSION

We tested the hypothesis that MRI structural lesions in the SIJ, especially fat metaplasia, predict new bone formation on spinal radiographs from patients with axial SpA in a prospective cohort. This was aimed at addressing a key preliminary requirement in the validation of a surrogate MRI biomarker for radiographic progression in the spine of patients with SpA. Our multivariate data demonstrates that the presence of definite ankylosis in the SIJ at baseline (as defined by an SSS score of ≥ 2 by both readers), and its extent, is significantly associated with new bone formation on spinal radiography on follow-up. The degree of subchondral fat metaplasia in the SIJ is also independently associated with radiographic progression in the spine. The lack of any new bone formation in the spine despite

prolonged symptom duration is associated with the absence of SIJ ankylosis and backfill. These data therefore support the hypothesis that structural lesions in the SIJ, specifically ankylosis and subchondral fat metaplasia, but not inflammation, predate and predict the development of new bone formation in the spine. The finding that fat metaplasia was independently prognostic for new bone in the spine in multivariate analyses adjusted for baseline mSASSS argues against the thesis that spinal progression is simply a reflection of advanced disease.

The association between inflammatory and structural lesions on MRI of the SIJ has been studied previously and helps to explain the associations observed in this study, which was focused on radiographic progression in the spine.^{2,3} The sequence of events evolves as follows: subchondral fat metaplasia develops as inflammation resolves in the bone marrow. When inflammation resolves at the site of erosion, new tissue that is bright on the T1W scan 'fills-in' the erosion cavity so that the erosion is no longer apparent. This new tissue has accordingly been termed backfill⁷ and SSS scores for backfill and erosion are therefore inversely associated. Fat metaplasia and backfill are followed by the development of SIJ ankylosis, and therefore MRI scores for these lesions are directly associated with SIJ ankylosis while MRI scores for erosion are inversely associated with SIJ ankylosis. This pattern of association with SIJ ankylosis is what we also observed with future development of spinal new bone in the current study.

The lack of a direct association between inflammation in the SIJ and development of spinal new bone might at first sight appear surprising because several studies have demonstrated a link between inflammation at vertebral corners on MRI and the development of new bone on radiography.⁴⁻⁶ However, this was primarily evident at vertebral corners where inflammation evolved into fat metaplasia. The presence of inflammation alone, and especially inflammation that resolved after institution of TNFi therapy but without development of fat metaplasia, did not predict development of new bone. This is consistent with the hypothesis that inflammation per se may not be the primary factor associated with new bone formation in the spine but a reparative phenotype characterised on MRI by the appearance of fat metaplasia and backfill after resolution of inflammation. While inflammation is an essential trigger for the eventual development of new bone, this work and that of others in imaging research consistently suggests that the immediate tissue repair response is more critical to the propensity for new bone. It is therefore further proposed that patients who demonstrate early features of fat metaplasia and backfill in the SIJ as inflammation resolves constitute the at-risk population for new bone formation in the spine.

When all definite MRI structural lesions, as defined by an SSS score ≥ 2 by both readers, were entered into the multivariate model, the presence of definite SIJ ankylosis

emerged as the primary lesion associated with radiographic progression in the spine. However, higher scores for SIJ fat metaplasia were also independently associated with radiographic progression in the spine. These observations may reflect the differences in specificity of limited structural lesions on MRI of the SIJ. A score of ≥ 2 for SIJ ankylosis is highly specific for SpA while limited areas of fat signal on T1W MRI can be seen in up to 40% of healthy individuals.¹⁹

Univariate analysis of predictors of radiographic progression in the spine confirmed previous reports of associations between CRP or ASDAS, and baseline mSASSS with progression^{8-10, 20-22} and also demonstrated new associations with fat metaplasia, erosion and ankylosis on SIJ MRI. However, only ankylosis and fat metaplasia on SIJ MRI were predictive when all clinical and imaging variables were entered into the multivariate model. Our data suggest that the association between SIJ fat metaplasia and new bone is more apparent in patients who have not been treated with TNFi, suggesting that TNFi agents may require further evaluation over longer time frames to determine whether these agents may influence the progression from fat metaplasia to new bone. Little is known about the histopathological basis for fat metaplasia, which is limited due to inaccessibility of tissue. A recent pathological analysis of facet joints from patients with long-standing AS has demonstrated subchondral fibroblastic tissue, which includes lipid within fibroblasts as well as macrophages, which invades the overlying cartilage as a precursor to the development of ankylosis.²³ The role of TNF in the development of this tissue and its invasive phenotype is unclear.

There are several limitations to this study that relate to its observational nature and relatively limited follow-up duration. In particular, longer time frames that permit a more reliable assessment of radiographic changes, data sampling at several time points, and analyses of the association between change in MRI lesions and change in progression adjusted for within-patient variation in the preceding time frame would enhance an understanding of the predictive capacity of structural lesions on MRI. The patients in this prospective cohort also had well-established disease with long symptom duration. However, assessment of patients in the early stages of SpA, especially non-radiographic axial SpA, will require very long periods of systematic follow-up in large study populations because new bone on spinal radiography will only develop in a small minority of patients in studies limited to just a few years of follow-up.

In conclusion, we have demonstrated that fat metaplasia and ankylosis in the SIJ on MRI are associated with an increased propensity for the future development of new bone in the spine of patients with SpA. Moreover, we demonstrate that these lesions are more important than either clinical or imaging parameters of inflammation in their association with the development of new bone. The finding that fat metaplasia was independently prognostic for new bone in the spine in multivariate

analyses adjusted for baseline mSASSS argues against the thesis that spinal progression is simply a reflection of advanced disease. Since these lesions can appear much sooner in SpA than new bone on radiography of the spine, they deserve further evaluation for their potential as lead prognostic indicators that could be imaging end points for studies of disease-modifying interventions.

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