The gestalt of spondyloarthritis: From early recognition to long-term imaging outcomes

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Chapter 9

Inflammation of the sacroiliac joints and spine on MRI predicts structural changes on MRI in axial spondyloarthritis: 5-year data from DESIR

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ABSTRACT

Objective: To test the impact of inflammation on MRI-structural changes occurring in the sacroiliac joints (SIJ) and the spine.

Methods: Patients with early axSpA from the DESIR cohort were included. MRIs of the SIJ (MRI-SIJ) and spine (MRI-spine), obtained at baseline, 2 and 5 years, were scored by 3 central readers. Inflammation and structural damage on MRI-SIJ/MRI-spine were defined by the agreement of ≥2 of 3 readers (binary outcomes), and by the average of 3 readers (continuous outcomes). The effect of inflammation (MRI-SIJ/MRI-spine) on damage (MRI-SIJ/MRI-spine, respectively) was evaluated in two models: i. Baseline prediction model: effect of baseline inflammation on damage assessed at 5-year; and ii. Longitudinal model: effect of inflammation on structural damage assessed during 5 years.

Results: 202 patients were included. Both the presence of bone marrow edema (BME) on MRI-SIJ and on MRI-spine at baseline were predictive of 5-year damage (≥3 fatty lesions) on MRI-SIJ [OR=4.2 (95% CI: 2.4; 7.3)] and MRI-spine [OR=10.7 (95% CI: 2.4; 49.0)], respectively, when adjusted for CRP. The association was also confirmed in longitudinal models (when adjusted for ASDAS) both in the SIJ [OR=5.1 (95% CI: 2.7; 9.6)] and spine [OR=15.6 (95% CI: 4.8; 50.3)]. Analysis of other structural outcomes (i.e. erosions) on MRI-SIJ yielded similar results. In the spine, a significant association was found for fatty lesions but not for erosions and bone spurs, which occurred infrequently over time.

Conclusion: We found a predictive and longitudinal association between MRI-inflammation and several types of MRI-structural damage in patients with early axSpA which adds to the proof for a causal relationship.

INTRODUCTION

Axial spondyloarthritis (axSpA) is a disease predominantly characterized by involvement of the axial skeleton. Axial involvement often translates into imaging abnormalities, which usually represent either an underlying inflammatory or structural lesion. Magnetic resonance imaging of the sacroiliac joints (MRI-SIJ) and spine (MRI-spine) is a modality to detect, quantify and evaluate (change of) axial inflammation in axSpA. Thus far, conventional radiographs have been prescribed for assessing progression of structural damage in clinical practice and research.

Patients with axSpA experience varying levels of radiographic progression (e.g. the occurrence of radiographic 'sacroiliitis' and new syndesmophytes).[1-4] Identifying patients with a higher likelihood of damage accrual is key to tailor treatment strategies early in the disease course. Elevation of C-reactive protein (CRP), disease activity as measured with the Ankylosing Spondylitis Disease Activity Score (ASDAS) and bone marrow edema (BME) on MRI-SIJ or MRI-spine have been shown to associate with increased probability of structural progression on conventional radiographs.[3, 5-12] However evidence is scarce in early disease and mostly limited to studies on which structural damage was measured with conventional radiographs.

The Interpretation of data stemming from the above-mentioned studies may be jeopardized by limitations of the instruments used to measure structural progression, especially at the SIJ level. It is well established that radiographic sacroiliitis defined by the mNY criteria is poorly reliable.[13-15] Investigators have been implementing strategies to improve the 'signal-to-noise' ratio by, for instance, combining judgments from ≥2 trained central readers.[3] Still, these strategies cannot fully eliminate the 'noise'.

In recent years there has been a growing interest in evaluating axial damage with other imaging modalities, such as MRI. Definitions for individual lesions (e.g. fatty lesions, erosions) have been proposed and composite scores validated.[16-19] Although MRI-detected lesions, as any outcome measure, are far from being error-free, available literature shows higher reliability for MRI-SIJ compared to pelvic radiographs in detecting structural lesions.[20] A better 'signal-to-noise' ratio, in theory, improves the ability to detect change and predictors thereof, especially in early disease where, at the group level, damage is known to be limited and to progress slowly.[3, 21]

Thus far, no study has assessed the effect of inflammation on structural damage evaluated on MRI. We aimed to test the effect of inflammation on several types of structural lesions both assessed by MRI and at the level of the SIJ and the spine in patients with early axSpA.

METHODS

Patients and study design

Five-year data from patients with early axSpA from the DEvenir des Spondylarthopathies Indifférenciées Récentes (DESIR) cohort have been used.[22] Patients had to have ≥2 consecutive MRI images (either of the SIJ or spine) during the 5-year follow-up to be included. The database used for the current analysis was locked on the 20th of June 2016. The study was conducted according to Good Clinical Practice guidelines and was approved by the appropriate

local ethics committees. Written informed consent had been obtained from participating patients before inclusion.

Imaging scoring procedures

MRI-SIJ and MRI-spine were performed at baseline for all patients. By protocol, at two and five years of follow-up MRIs were only performed in participating centres in Paris (n=9 out of the 25 participating centers). Each image was independently scored by 3 trained central readers blinded to chronology and clinical data. MRI-SIJ and MRI-spine were performed on a 1-1.5T scanner providing T1-weighted Turbo Spin-Echo (T1-w) and Short Tau Inversion Recovery (STIR) sequences. Scanning was performed in a coronal oblique plane for SIJ and in a sagittal plane for spine, with a slice thickness of 4mm. A detailed description of the MRI protocol in DESIR has been previously reported.[23, 24]

Structural damage on MRI

The Spondyloarthritis Research Consortium of Canada (SPARCC) MRI-SIJ Structural score by Weber *et al* was used to define individual structural lesions on MRI-SIJ.[18] In the absence of a formal definition for structural damage on MRI-SIJ, we considered 3 definitions previously shown most discriminatory between axSpA and no axSpA: ≥5 fatty lesions and/or erosions; ≥3 erosions; and ≥3 fatty lesions.[25] Continuous structural lesions on MRI-SIJ were defined as number of erosions, number of fatty lesions (both range: 0-40), number of fatty lesions and/or erosions (range: 0-80), and as the total number of lesions including fatty lesions, erosions, partial ankylosis / total ankylosis with the addition of sclerosis (not in the original score) (range: 0-144).

Structural lesions on MRI-Spine were scored according to the Canada–Denmark (CANDEN) method, modified to include only corner lesions.[16, 17] Similar to MRI-SIJ, in absence of a formal definition, we defined structural damage on MRI-spine as ≥5 fatty lesions, which has been previously shown highly specific for axSpA.[25, 26] In addition, we also considered ≥5 fatty lesions and/or erosions; ≥3 erosions; ≥3 fatty lesions; and ≥3 bone spurs. The total number of fatty lesions, erosions, bone spurs (range: 0-92; for each), fatty lesions and/or erosions (range: 0-184) and the total number of structural lesions (fatty lesions, erosions, bone spurs, including also ankylosis; range: 0-322) was assessed, as continuous structural outcomes.

Inflammation on MRI

Inflammation on MRI-SIJ was assessed using the Assessment of SpondyloArthritis international Society (ASAS)-definition (positive/negative) and the SPARCC-score (range: 0-72).[27-29] BME on MRI-Spine was defined according to the ASAS definition (≥3 vertebral corner lesions; positive/negative).[30] In addition, a cut-off of at least 5 lesions was assessed, as it has been shown to be highly specific of axSpA.[25] The total spine SPARCC score was used as a continuous inflammatory outcome (range: 0-414).[31]

The interreader reliability of the MRI scores used in this study has been reported elsewhere.[32]

Statistical analysis

Structural progression of binary scores was assessed in clinically relevant subgroups according to the CRP and BME status at baseline, and defined by the agreement of ≥2 out of 3 readers as the percentage of net progression: the number of 'progressors' (change from negative to positive) minus the number of 'regressors' (change from positive to negative) divided by the total number of patients, a method previously described in detail.[33]

The effect of inflammation, both on MRI-SIJ and MRI-spine, on structural outcomes, again both on MRI-SIJ and MRI-spine, respectively, was evaluated by two types of generalized estimating equations (GEE) models: i. a baseline model: effect of baseline inflammation on 5 years structural damage incorporating measurements from all readers (1-level GEE model adjusted for reader); and ii. A longitudinal model: effect of BME at *t* on structural outcomes at *t+1* over 5 years (longitudinal time-lagged 2-level GEE models with auto-regression). Binary variables of Inflammation (i.e. BME) were modelled using binary damage outcomes (binomial GEE), while continuous variables of inflammation (i.e. SPARCC) were modelled using continuous outcomes of damage (linear GEE).

Table 1. Baseline patient and disease characteristics comparing patients with MRI available in ≥2 consecutive (included) visits to those without (excluded)

	MRI on ≥2 consecutive visits (N=202)	MRI on <2 consecutive visits (N=60)
Age at baseline (years)	34 (9)	33 (8)
Male gender	96 (48)	27 (45)
Symptom duration (years)	2 (1)	1 (1)
HLA-B27	125 (62)	32 (53)
ASAS axSpA criteria	133 (66)	35 (60)
Sacroiliitis on MRI-SIJ† (ASAS)	58 (29)	15 (28)
BME on MRI-Spine† (ASAS)	14 (7)	3 (6)
≥ 5 BME lesions on MRI-spine	10 (5)	2 (4)
Radiographic sacroiliitis† (mNY)	25 (13)	8 (14)
≥ 3 fatty lesions on MRI-SIJ	23 (12)	7 (14)
≥ 3 erosions on MRI-SIJ	29 (15)	9 (17)
≥ 3 fatty lesions on MRI-spine	3 (2)	0 (0)
≥ 3 erosions on MRI-spine	0 (0)	0 (0)
≥ 3 bone spurs on MRI-spine	0 (0)	0 (0)
BASDAI (0-10)	4 (2)	47 (21)
ASDAS-CRP	3 (1)	3 (1)
Elevated CRP (≥6 mg/L)	52 (27)	12 (21)
BASFI£ (0-10)	3 (2)	33 (28)
Treatment with NSAIDs	192 (95)	57 (95)
Treatment with TNFi	0 (0)	0 (0)

Values are mean (SD) for continuous variables and number (percentage) for dichotomous variables. * Independent samples t-test for continuous and Chi2 for dichotomous variables; † agreement between 2 out of 3 readers; <5% missing data: mNY, BME on MRI-spine (ASAS), ≥ 5 BME lesions on MRI-spine, ≥ 3 fatty lesions on MRI-spine, ≥ 3 erosions on MRI-spine, ≥ 3 bone spurs on MRI-spine, ASDAS, CRP; <1% missing data: sacroiliitis on MRI-SIJ, ≥ 3 fatty lesions on MRI-SIJ, ≥ 3 erosions on MRI-SIJ, BASDAI, BASFI. MRI, magnetic resonance imaging; SIJ, sacroiliac joints; ASAS, Assessment of SpondyloArthritis international Society; mNY, radiographic sacroiliitis according to the modified New York criteria; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; ASDAS, Ankylosing Spondylitis Disease Activity Score; CRP, C-reactive protein; BASFI, Bath Ankylosing Spondylitis Functional Index; NSAID, non-steroidal anti-inflammatory drugs; TNFi, tumor necrosis factor inhibitors; NA, not applicable

The final multivariable models included variables that were found to confound the association of interest (i.e. that importantly changed the effect of inflammation on structural outcomes). The following variables were tested as possible confounders: age (in years), gender (male vs female), HLA-B27 (positive vs negative), smoking status (smoker vs non-smoker), CRP (mg/L), Bath Ankylosing Spondylitis Activity Index (BASDAI), Ankylosing Spondylitis Disease Activity Score (ASDAS) (BASDAI plus CRP and ASDAS tested in separate models to avoid collinearity), treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) (yes/no) and tumor necrosis factor inhibitors (TNFi) (yes/no). Variables with a potential to change over time were modelled as such (i.e. all the above except gender and HLA-B27) in the longitudinal models

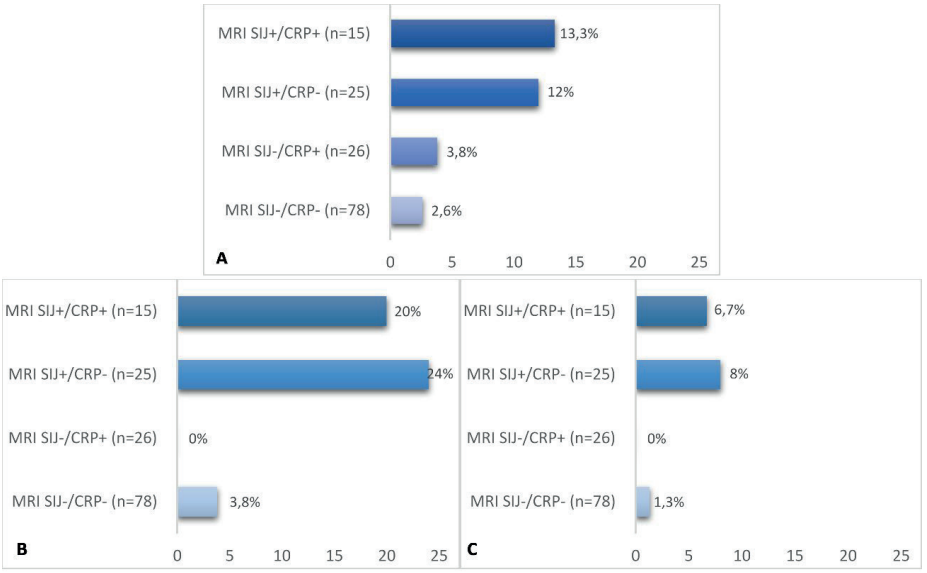

Figure 1. Net progression from MRI-SIJ without structural lesions (MRI-SIJ-STR negative) to MRI-SIJ with structural lesions (MRI-SIJ-STR positive) defined by **(A) ≥5 fatty lesions and/or erosions, (B) ≥3 fatty lesions and (C) ≥3 erosions**, according to baseline objective inflammatory markers (MRI-SIJ inflammation and CRP); MRI-SIJ+: Presence of bone marrow edema on MRI-SIJ according to the ASAS definition, CRP+: CRP ≥6 mg/l at baseline. Net progression from MRI-SIJ-STR negative to MRI-SIJ-STR positive at year 5: number of 'progressors' minus the number of 'regressors' divided by the total number of patients in each category (N=144; MRI-SIJ available both at baseline and year 5 and CRP available at baseline). MRI, magnetic resonance imaging; SIJ, sacroiliac joints; STR, structural; CRP, C-reactive protein.

RESULTS

Baseline characteristics

Of the total 708 patients from DESIR, 262 could have imaging at follow-up according to the protocol and 202 had at least 2 consecutive visits with data available either on MRI-SIJ or MRI-Spine (196 had both modalities, 3 had MRI-SIJ only and 3 had MRI-Spine only) and were therefore included. No significant baseline differences were found between patients included and not included in this study (Table 1). The presence of BME at baseline was more frequent in the SIJ (29%) than in the spine [7% (ASAS definition); 5% for ≥5 BME lesions]. Likewise, structural

damage was higher in the SIJ (e.g. ≥3 fatty lesions on MRI-SIJ: 12%) than in the spine (e.g. ≥3 fatty lesions on MRI-spine: 2%).

Table 2. Effect of MRI inflammation on MRI structural damage in the SIJ (multivariable models)

Binary scores	≥5 fatty lesions/erosions OR (95% CI)	≥3 fatty lesions OR (95% CI)	≥3 erosions OR (95% CI)
BME at baseline† (N=144-151)	**5.6 (3.1; 10.0)***	**4.2 (2.4; 7.3)***	**4.1 (2.1; 7.8)**
BME over 5 years‡ (N=197-199)	**7.7 (4.5; 13.4)¥**	**5.1 (2.7; 9.6)¥**	**3.2 (1.9; 5.3)**
Continuous scores	Fatty lesions/erosions β (95% CI)	Fatty lesions β (95% CI)	Erosions β (95% CI)
SPARCC at baseline† (N=144-151)	**0.23 (0.15; 0.31)***	**0.12 (0.05; 0.19)***	**0.12 (0.06; 0.18)**
SPARCC over 5 years‡ (N=197-199)	**0.13 (0.07; 0.19)¥**	**0.10 (0.04; 0.16)¥**	**0.04 (0.01; 0.06)**

† Multilevel GEE models: effect of inflammation at baseline on the outcome at 5 years taking the scores from the individual readers into account, ‡ longitudinal multilevel time-lagged GEE models with autoregression (i.e. effect of inflammation at *t* on the outcome at *t+1* adjusted for the outcome at t, taking the scores from the individual readers into account); * Adjusted for CRP at baseline; ¥ Adjusted for time-lagged ASDAS-CRP. BME, bone marrow edema according to the ASAS definition (positive/negative); MRI-SIJ, magnetic resonance of the sacroiliac joints; SPARCC, spondyloarthritis research consortium of Canada; ASDAS, Ankylosing Spondylitis Disease Activity Score; CRP, C-reactive protein.

Structural progression according to the presence of objective inflammation at baseline

In total, 155 patients had complete MRI data at baseline and 5 years (141 both modalities, 10 MRI-SIJ only and 4 MRI-Spine only). Net progression, defined by ≥ 5 fatty lesions and/or erosions, ≥3 fatty lesions and ≥3 erosions on MRI-SIJ, according to baseline objective inflammatory markers is shown in Figure 1. Patients with BME on MRI-SIJ present at baseline had higher net progression rates compared to those that were BME negative for all outcomes, irrespective of the CRP status (range if BME positive: 7% to 24%; range if BME is negative: 0% to 4%). On MRI-spine overall net progression was -0.7% both for ≥5 fatty lesions and/or erosions and for ≥5 fatty lesions; 0.7% for ≥3 fatty lesions and 0% for ≥3 erosions and for ≥3 bone spurs. These low numbers precluded further analysis according to the presence of inflammatory markers at baseline.

Effect of inflammation on structural progression (multivariable models)

Sacroiliac joints

The presence of BME on MRI-SIJ at baseline was predictive of the development of fatty lesions and erosions on MRI-SIJ 5 years later for all binary definitions [range odds ratio (OR): 4.1-5.6], after adjustment for CRP at baseline (Table 2). Similar results were found in the longitudinal models (after adjustment for ASDAS). On average, patients with BME on MRI-SIJ had a 5 times higher likelihood of having at least 3 fatty lesions in the subsequent visit as compared to those without BME [OR (95% CI): 5.1 (2.7; 9.6)] (Figure 2). The association between the continuous SPARCC score on MRI-SIJ and the various continuous structural outcomes was also always statistically significant, and present in both models.

Spine

Testing the association of interest on MRI-spine was hampered by low number of lesions, leading to imprecise estimates and, for some outcomes (i.e. ≥3 erosions and ≥5 fatty lesions/erosions), precluded the estimation of the effect (Table 3). Only the association between BME and ≥3 fatty lesions was statistically significant. The presence of baseline BME (ASAS definition) on MRI-spine was positively associated with ≥ 3 fatty lesions at 5 years on MRI-spine [OR (95% CI): 10.7 (2.4; 15.6)]. This effect was also positive in the longitudinal model [OR (95% CI): 15.6 (4.8; 50.3)] (Figure 2). As in MRI-SIJ, CRP (baseline models) and ASDAS (longitudinal models) have been found to confound the association of interest. Testing the effect of ≥5 BME lesions yielded similar results, but with wider 95% CI (Online Supplementary Table S1). For continuous variables a positive association could be found for fatty lesions alone or in combination with erosions, but not for erosions alone and bone spurs, both in baseline and longitudinal models.

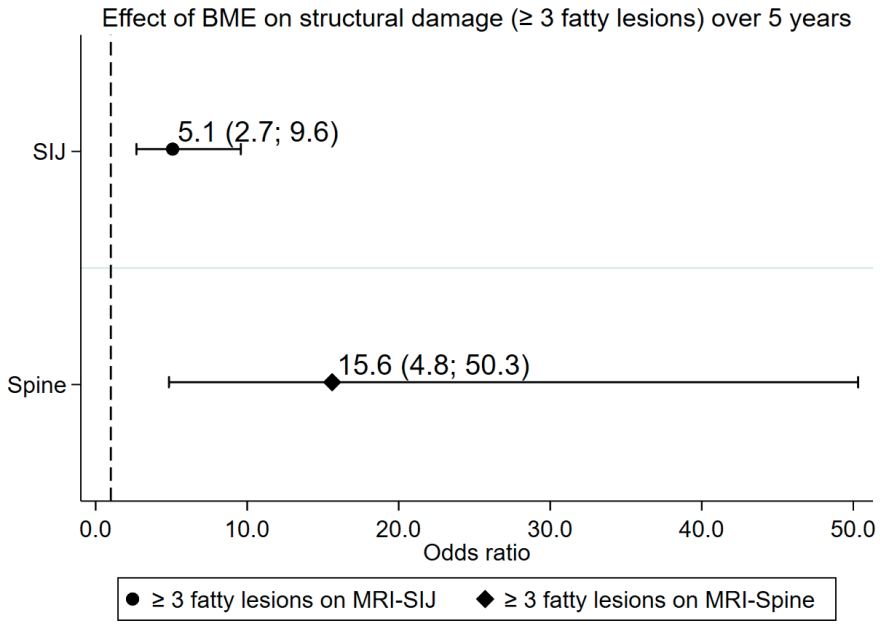

Figure 2. Effect of BME (according to the ASAS definition) on structural damage (defined as ≥3 fatty lesions) both in the SIJ and spine (longitudinal time-lagged models with autoregression). BME, bone marrow edema; ASAS, Assessment of SpondyloArthritis international Society; BME, bone marrow edema; SIJ, sacroiliac joints; MRI, magnetic resonance imaging.

Table 3. Effect of MRI inflammation on MRI structural damage in the spine (multivariable models)

Binary scores	≥5 fatty lesions/erosions	≥ 5 fatty lesions	≥3 fatty lesions	≥3 erosions	≥3 bone spurs
BME at baseline† (N=139)	¥	¥	**10.7 (2.4; 49.0)***	¥	3.2 (0.4; 27.8)*
BME over 5 years‡ (N=197)	¥	0.9 (0.8; 1.2)£	**15.6 (4.8; 50.3)£**	¥	2.8 (0.8; 9.6)£
Continuous scores	Fatty lesions/erosions	Fatty lesions		Erosions	Bone spurs
SPARCC at baseline† (N=139-145)	**0.10 (0.01; 0.18)***	**0.08 (0.02; 0.14)**		0.02 (0.00; 0.03)†	0.01 (-0.01; 0.03)†
SPARCC over 5 years‡ (N=197)	**0.06 (0.02; 0.11)£**	**0.07 (0.02; 0.11)£**		0.00 (-0.01; 0.01)£	0.01 (0.00; 0.02)

† Multilevel GEE model (i.e. effect of inflammation at baseline on the outcome at 5 years taking the scores from the individual readers into account), ‡ longitudinal multilevel time-lagged GEE models with autoregression (i.e. effect of inflammation at t on the outcome at *t+1* adjusted for the outcome *at t*, taking the scores from the individual readers into account); * Adjusted for CRP at baseline; £ Adjusted for time-varying lagged ASDAS-CRP. BME, bone marrow edema according to the ASAS definition (≥3 lesions; positive/negative); MRI-Spine, magnetic resonance of the spine; ¥ model fails to converge due to low number of events. SPARCC, spondyloarthritis research consortium of Canada; ASDAS, Ankylosing Spondylitis Disease Activity Score; CRP, C-reactive protein; ASAS, Assessment of SpondyloArthritis international Society.

DISCUSSION

In this prospective observational cohort study, we have shown that axial inflammation detected on MRI predicts subsequent development of structural lesions (especially fatty lesions) also on MRI over 5 years in patients with early axSpA. This effect is independent of systemic inflammation and is seen both at the SIJ and spinal level but is measured more precisely in the SIJ where damage prevails in early disease. Our results add to the existing evidence by showing that the association between axial inflammation and some lesions reflecting structural damage can be measured with MRI in patients with early axSpA.

In the current study we have demonstrated an association between local inflammation and structural damage both measured on MRI in patients with early axSpA. Involvement of the axial skeleton in axSpA usually starts at the SIJ level.[21, 34, 35] In line with the literature, we found that 6 times more patients showed structural damage (e.g. ≥ 3 fatty lesions) on MRI-SIJ (12%) than on MRI-spine (2%) at baseline. Consequently, the longitudinal association between BME and structural damage (e.g. ≥3 fatty lesions) on MRI-SIJ [OR 5.1 (95% CI: 2.7; 9.6)] was found with a substantially higher precision (narrower confidence intervals) compared to the same effect in the spine [OR: 15.6 (95% CI 4.8; 50.3)]. Although it may seem that the effect of inflammation on damage is stronger on the spine than on the SIJ (OR: 16 vs 5), this is not necessarily the case. It is well-known that imprecise estimates tend to overestimate effect-sizes.[36]

Evidence that inflammation on MRI drives structural damage in early axSpA is relevant to the practicing rheumatologist since it argues in favor of its use for prognostic stratification. In addition, if inflammation drives damage, it is logical to expect that interventions targeting the former will prevent, or at least retard, the latter. However, thus far, trial data do not support this claim.[37] The complex, and yet not fully understood, pathophysiology of new bone formation in axSpA may, at least in part, explain this disappointing result. For instance, it has been shown that systemic inflammation, measured by ASDAS, predicts spinal radiographic progression in radiographic axSpA (r-axSpA).[6, 8] However, progression was still found in patients with inactive disease. Similarly, in another study, inflammation at the vertebral unit level increased the likelihood of the formation of a new syndesmophyte in the same location 2 years later, but most new syndesmophytes appeared in vertebral units without signs of inflammation.[12] These data highlight the relevance of inflammation in driving structural progression but also suggest that other mechanisms may play a role.

However, biology cannot fully explain the failure of anti-inflammatory drugs in modifying the effect of inflammation on structural damage. Outcome measures (lack of) sensitivity to change, has also been previously proposed as a likely explanation.[38] If an intervention truly prevents further damage by reducing inflammation (or by any other means), low sensitivity to change of the outcome measure may prevent that such effect becomes evident (e.g. no significant difference between active drug and placebo). Thus far, progression of structural damage has been mostly measured in conventional radiographs, with mSASSS and the mNY grading system as the most often used outcomes in the spine and SIJ, respectively. However, both the mSASSS and the mNY have low sensitivity to change and assessing radiographic progression with the latter is further challenged by its poor reliability.[3, 14, 15, 39] It remains to be proven that structural lesions detected on MRI are more sensitive to change than those on radiographs.

However, our study supports that different lesions may yield different results. For instance, compared with erosions or bony spurs, fatty lesions were more prevalent in our early axSpA population, especially in the SIJ leading to more precise estimates. Thus, our data may inform future research aiming at clarifying whether MRI is valid alternative to conventional radiography in detecting structural treatment effects in patients with axSpA.

Our study is not without limitations. First, Inflammatory and structural lesions, per patient, were read together by the same reader, which may obviously result in overestimating the association between both. This contrasts with other studies where inflammation and damage were blindly measured with different imaging modalities. However, it should be stressed that readers were still blinded to time-order. That is, they did not know if a certain lesion (e.g. BME) pertained to a baseline or to a follow-up image. Thus, 'causality by reading' though not impossible, is unlikely to fully explain the impressive associations found in our study. Second, the lack of an association between vertebral corner inflammation on MRI-spine and erosions and bone spurs, should be interpreted with caution. Even though a 'true' lack of association cannot be ruled out, as mentioned above, this may be also due to low statistical power driven by low number of these lesions in the spine. The role of inflammation on sites other than vertebral corners for the progression of spinal damage should be addressed in future studies.

In summary, we have shown that local inflammation is associated with development of structural damage (e.g. fatty lesions), both measured with MRI, over 5 years in the SIJ and spine in early axSpA. This association is detected with more precision on the SIJ where structural damage prevails, compared to the spine, in early disease. These findings support the concept that MRI is a valid alternative to conventional radiographs in detecting the structural consequences of axial inflammation in patients with early axSpA.

SUPPLEMENTARY DATA

Supplementary data are published online on the website of Arthritis Care & Research

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