Bone marrow edema in the sacroiliac joints is associated with the development of structural lesions at the same anatomical location over time in patients with axial spondyloarthritis

Rodrigues-Manica, S.; Sepriano, A.; Ramiro, S.; Landewe, R.; Claudepierre, P.; Molto, A.; ... ; Heijde, D. van der

Seminars in Arthritis and Rheumatism 61 (2023) 152225

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit

Bone marrow edema in the sacroiliac joints is associated with the development of structural lesions at the same anatomical location over time in patients with axial spondyloarthritis

Santiago Rodrigues-Manica [a,b,*], Alexandre Sepriano [b,c], Sofia Ramiro [c,d,e], Robert Landewé [f,d], Pascal Claudepierre [g], Anna Moltó [h,i], Maxime Dougados [h,i], Miranda van Lunteren [c], Désirée van der Heijde [c]

[a] Department of Rheumatology, Hospital Egas Moniz, Centro Hospitalar Lisboa Ocidental, Lisbon, Portugal
[b] CEDOC, NOVA-Medical School, Lisbon, Portugal
[c] Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands
[d] Department of Rheumatology, Zuyderland Medical Center, Heerlen, The Netherlands
[e] NOVA Medical School, Universidade Nova de Lisboa, Lisbon, Portugal
[f] ARC, Amsterdam, The Netherlands
[g] Hopital Henri Mondor, Universite Paris Est Creteil, Service de Rhumatologie, EA 7379 – EpidermE, AP-HP, Creteil, France
[h] Rheumatology Department, Cochin Hospital, APHP, Paris, France
[i] INSERM U-1153, CRESS, Université Paris-Cité, Paris, France

ARTICLE INFO

Keywords:
(axSpA
MRI
Radiography
Imaging
Progression)

ABSTRACT

Objective: To assess whether the presence of bone marrow edema (BME) leads to the development of structural lesions at the same anatomical location of the sacroiliac joints (SIJ), and to investigate the association between BME patterns over time and structural lesions in patients with early axial spondyloarthritis (axSpA).
Methods: Patients with axSpA from the DESIR cohort with ≥2 consecutive magnetic resonance imaging (MRI)-SIJ were assessed at baseline, 2 and 5 years. MRI-SIJ images were divided into 8 quadrants. The association between BME and subsequent structural lesions (sclerosis, erosions, fatty lesions, and ankylosis) on MRI in the same quadrant was tested longitudinally. Additionally, patients were grouped according to the pattern of BME evolution across quadrants over time (no BME, sporadic, fluctuating, and persistent). The association between these patterns and 5-year imaging outcomes (eg: ≥5 erosions and/or fatty lesions on MRI-SIJ) was tested.
Results: In total, 196 patients were included. BME in each quadrant was associated with sclerosis (OR:1.9 (95%CI: 1.1;3.4)), erosions (1.9 (1.5;2.5)) and fatty lesions (1.9 (1.4;2.6)). Ankylosis was uncommon. There was a gradient between increased level of inflammation and subsequent damage: compared to the 'no BME' pattern, the sporadic (OR (95% CI): 2.1 (1.0;4.5)), fluctuating (OR:5.6(2.2;14.4)) and persistent (OR:7.5(2.8;19.6)) patterns were associated with higher structural damage on MRI-SIJ at 5-years.
Conclusions: In early axSpA, inflammation on MRI-SIJ leads to damage at the quadrant level. The higher the exposure to inflammation across quadrants in the SIJs over time the higher the likelihood of subsequent structural damage, suggesting a cumulative effect.

Introduction

Bone marrow edema (BME) detected on magnetic resonance imaging (MRI) is the imaging translation of an acute inflammatory lesion. BME can occur both in the subchondral bone of the sacroiliac joints (SIJ) and in the corners of the vertebrae in patients with axial Spondyloarthritis (axSpA) [1]. The diagnostic value of BME on magnetic resonance imaging of the SIJ (MRI-SIJ) is well known [1].

Our understanding of the prognostic role of acute inflammation has also increased substantially over the years. Patients with axSpA with acute lesions on the MRI-SIJ are more likely to respond to therapy than patients without acute lesions [2]. Also, several studies have shown that

* Corresponding author.
E-mail address: santiagorodriguesma@gmail.com (S. Rodrigues-Manica).

https://doi.org/10.1016/j.semarthrit.2023.152225

Available online 18 May 2023

the presence of BME predicts pathological new bone formation in radiographs of the sacroiliac joints (SIJ) [3,4]. However, these analyses were conducted at the level of the SIJ, irrespective of the location of BME and new bone formation, which could theoretically take place in different quadrants.

Available therapeutic options are effective in reducing BME [5]. Thus, in theory, suppressing BME should at least retard the formation of structural lesions [6]. However, definitive evidence supporting this claim is yet to be produced. In truth, the pathophysiology of new bone formation in axSpA is still poorly understood. It is believed that once inflammation disappears it ignites a repair mechanism that leads to structural damage (i.e. bony bridges) [7]. Studies looking at the effect of BME on the subsequent formation of new syndesmophytes in the same location are in agreement with this hypothesis, but the effect-size is rather small [8].

The evidence informing the prognostic value of individual BME lesions in the SIJ is more limited. In fact, thus far no study has investigated whether BME is linked to a structural lesion in the same anatomical location in the SIJ. In addition, the location of BME in the SIJ may vary over time, and it might appear and disappear more than once in the same patient [9]. However, the effect of such fluctuations on the burden of the disease has not yet been determined.

Therefore, we decided to investigate the prognostic significance of BME in the SIJ of patients with axSpA. Our aims were twofold: i. to assess whether there is an association between BME and subsequent development of structural lesions in the same anatomical location; and ii. to determine whether there is an association between the evolution pattern of BME-SIJ over time and long-term structural outcomes.

Methods

Patients and study design

Patients with early axSpA from the *Devenir des Spondyloarthropathies Indifférenciées (*DESIR) cohort (clinicaltrials.gov: NCT 0164 8907) were included. DESIR has been previously described in detail [10]. Briefly, consecutive patients, aged 18 to 50 from 25 centers in France, with inflammatory back pain for at least 3 months but less than 3 years, for whom the treating rheumatologist considered the symptoms suggestive of axSpA (a score $\geq$5 on a scale from 0 to 10) were included between December 2007 and April 2010. Each patient was followed every 6 months up to 2 years, and yearly thereafter up to 5 years. In the current study, only patients with at least 2 consecutive MRI-SIJ available were included (baseline required). By protocol, at two and five years of follow-up, MRIs were only performed in participating centers in Paris (n = 9 out of the 25 participating centers), which means that only these patients could be eligible for this study. The study was conducted according to good clinical practice guidelines and was approved by the appropriate local medical ethical committees. Written informed consent had been obtained from participating patients before inclusion.

Imaging acquisition

Radiographs (SIJ and spine) and MRI-SIJ images were obtained at baseline (for all patients), 2 years, and 5 years. MRI-SIJ 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, with a slice thickness of 4 mm. A detailed description of the MRI protocol in DESIR has been previously reported [11]. Each radiograph and MRI image was independently scored by three independent central readers, blinded to clinical data and to the results of other imaging modalities and without known chronology.

Structural outcomes

We used structural outcomes in the SIJ, both on MRI and radiographs, and in the spine, assessed with radiographs. On the MRI-SIJ, each side of the SIJ (left/right) was divided into quadrants (Q1 to Q4): Q1 corresponds to upper iliac, Q2 to upper sacral, Q3 lower sacral, and Q4 to lower iliac. The dichotomic presence of each elementary lesion, namely sclerosis, erosions, fatty lesions, and ankylosis in each quadrant and each slice according to previously published definitions [12]. Presence or absence of each lesion was defined in each quadrant, as a binary variable, taking all slices into account.

Radiographic structural damage of the SIJ was measured with the modified New York (mNY) grading system as a binary (mNY positive/mNY negative) and a continuous variable (the total score ranges from 0 to 8, and is composed of the sum of the two sides of the SIJ, each side ranges 0–4) [13], and structural damage of the spine was assessed according to the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) (0–72) [14].

Main variable of interest – Inflammation (bone marrow edema) on MRI-SIJ

The dichotomic presence of each elementary BME was assessed in each quadrant (defined in the same way as explained for structural outcomes) and in each visit according to the ASAS definition [12].

Additionally, for patients who had MRI-SIJ performed at all three time points, four mutually exclusive groups were created according to the pattern of BME observed when assessing the evolution of BME in all 8 quadrants over the 5 years: i. “no BME”, was defined when none of the quadrants ever presented BME; ii. “fluctuating”, when one of the two scenarios was present: either SIJ-BME was present at a given quadrant at baseline, absent at 2 years and present again at 5 years or if BME was present only at 2 years; iii. “persistent” if BME was present in the same quadrant, in at least one of the 8 quadrants, in all time points, regardless of other quadrants; and iv. “sporadic”; when BME neither changed between being present and absent nor was persistently present or absent across visits; that is, when the BME pattern did not fulfill any of the former definitions.(Fig. 1)

Each elementary lesion was considered to be present or absent according to the assessment of each individual reader. For descriptive purposes only, aggregated scores were computed based on the mean of the three readers for continuous variables and 2 out 3 readers agreement for dichotomous variables.

Additional clinical variables

Disease activity was assessed with the Ankylosing Spondylitis Disease Activity Score (ASDAS) [15]. Treatment with non-steroidal anti-inflammatory drugs (NSAIDs), oral steroids, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), and tumor necrosis factor inhibitors (TNFi) was also recorded as yes/no in each visit. C-reactive protein (CRP) and smoking status (current smoker/non-current smoker) as well. Information on age, gender, human leukocyte antigen B27 (HLA-B27) status, and symptom duration (in years) was collected at baseline.

Statistical analysis

The longitudinal association between BME and the subsequent formation of each of the elementary structural lesions (erosion, sclerosis, fatty lesion, and ankylosis) in the same quadrant was tested in time-lagged multilevel (reader, patient, quadrant) GEE models with autoregression, considering individual reader data and with an exchangeable working correlation structure to handle repeated measures over time. Time-lagged models were run so that the relationship between BME at one-time point and the structural lesions in the subsequent time point

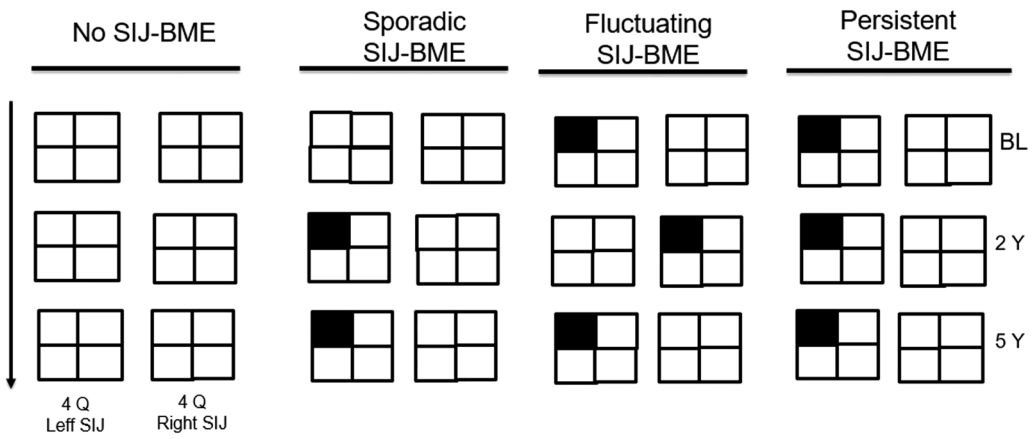

Fig. 1. Patterns of bone marrow edema (BME) distribution over time when considering all simultaneous quadrants of the sacroiliac joints (SIJ) over time
Black square: BME presence; White square: BME absence; Q: quadrant; BL: Baseline; 2Y: 2 years; 5Y: 5 years.

could be analysed, bringing the temporal relationship into the analysis. Time-lagged models refer to the inclusion of the variable of interest in the previous time point compared to the time point of the outcome (e.g. BME at year 2 as the time-lagged variable of interest and analysing its effect on erosions at the subsequent time point, i.e. at year 5). Autoregressive models mean that they were adjusted for the corresponding structural lesions (i.e. outcome) in the previous time point.

The effect of the BME pattern on 5-year imaging outcomes (mNY, mSASSS, and, on MRI-SIJ, the presence of ≥5 erosions and/or fatty lesions, ≥3 erosions, and ≥3 fatty lesions) was evaluated using individual reader scores, for both the BME pattern and the imaging outcomes, in multilevel (reader and patient) generalized estimating equations (GEE) models (assuming an exchangeable correlation structure).

All models (for both types of analyses described) were adjusted for gender, symptom duration, presence of HLA-B27, smoking status, ASDAS and treatment (NSAID, csDMARD, bDMARD).

Sensitivity analyses

The analysis was repeated: (i). including only patients with a clinical diagnosis who also fulfilled the ASAS classification criteria for axSpA; (ii). including only patients for whom there was certainty for the clinical diagnosis of axSpA >7; (iii). Including only patients who during follow-up, in contrast with baseline, were considered not to have axSpA and; (iv). using CRP, instead of ASDAS, as a confounder.

Results

From the 262 eligible patients, 196 had an MRI-SIJ in at least two consecutive visits and were therefore included. The mean age was 38 years (SD 9) and 48% were male (Table 1). Baseline characteristics were similar between the included ($n = 196$) and excluded patients ($n = 512$) (Online Supplementary Table S1). Most of the patients received treatment with NSAIDs at baseline (95%) and almost half (49%) were treated with a TNFi at least once after the baseline visit.

Table 1
. Baseline characteristics of all patients and according to the BME pattern.

	All patients ($n = 196$)	Patients with 3 MRIs ($n = 136$)	No BME ($n = 63$/136;46%)	Sporadic ($n = 34$/136;25%)	Fluctuating ($n = 21$/136;15%)	Persistent ($n = 18$/136;13%)	p-value§
Age (years)	38 (9)	34 (9)	35 (10)	34 (8)	31 (8)	34 (9)	0.35
Male gender (%)	95 (48)	68 (50)	31 (40)	15 (44)	9 (43)	13 (72)	0.22
Symptom duration (years)	1.5 (0.9)	1.5 (0.8)	1.4 (0.8)	1.5 (1.0)	1.5 (0.9)	1.6 (0.9)	0.95
HLA-B27 (%)	121 (61)	85 (63)	33 (52)	22 (65)	18 (86)	12 (67)	0.05
ASAS axSpA classification criteria (%)	128 (65)	90 (67)	32 (51)	24 (73)	18 (86)	16 (89)	<0.01
Smokers (%)	74 (38)	51 (38)	21 (33)	13 (38)	7 (33)	10 (56)	0.37
ASDAS-CRP*	2.6 (0.9)	2.7 (0.9)	2.9 (0.9)	2.8 (0.9)	2.1 (0.8)	2.4 (0.9)	<0.01
BASDAI (0–10)	4.3 (2.0)	4.4 (2.0)	5.1 (1.7)	4.7 (2.0)	3 (1.6)	3.4 (2.1)	<0.01
CRP (mg/L)*	7.5 (11.8)	7.9 (12.5)	7.5 (15.1)	10.3 (10.8)	6.3 (7.8)	6.4 (9.2)	0.03
NSAIDs (%)	187 (95)	129 (95)	59 (94)	33 (97)	21 (100)	16 (89)	0.40
Oral steroids (%)	23 (12)	19 (14)	8 (13)	6 (18)	2 (10)	3 (17)	0.82
csDMARDs (%)	28 (14)	25 (18)	16 (25)	4 (12)	3 (14)	2 (11)	0.27
mNY (%)*	39 (20)	19 (15)	6 (10)	4 (13)	3 (15)	6 (35)	0.07
mNY grading (0–8)*	1.3 (1.6)	1.4 (1.8)	0.8 (1.3)	1.4 (1.6)	1.9 (2.0)	2.7 (2.3)	<0.01
Presence of MRI-SIJ BME (%)	58 (29)	41 (30)	0 (0)	14 (41)	11 (52)	18 (100)	<0.01
≥ 5 fatty lesions or erosions on MRI-SIJ (%)	30 (15)	22 (16)	4 (6)	8 (24)	4 (19)	6 (33)	0.02
mSASSS (0–72)*	0.5 (1.8)	0.6 (1.9)	0.5 (1.0)	0.5 (1.0)	0.5 (0.7)	1.7 (4.7)	0.97

Values are mean (standard deviation) for continuous variables and number (%) for categorical variables. §For categorical variables chi2 was used; for continuous variables Kruskal-Wallis H test was used.

* 5–10% of patients with missing data. BME: bone marrow edema; HLA-B27: Human leukocyte antigen B27;ASAS axSpA: axial spondyloarthritis according to the Assessment of SpondyloArthritis international Society; CRP: C reactive protein;ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score CRP; BASDAI: The Bath Ankylosing Spondylitis Disease Activity Index; mSASSS: modified Stoke Ankylosing Spondylitis Spinal Score; NSAIDs: non-steroidal anti-inflammatory drugs; csDMARDs: conventional synthetic disease modifying antirheumatic drugs; mNY: modified New York criteria; MRI-SIJ: magnetic resonance imaging of the sacroiliac joints. TNFi: tumor necrosis factor inhibitor.

BME and fatty lesions were evenly distributed across quadrants, while erosions and sclerosis occurred preferably in the iliac side (Q1 and Q4). BME decreased over time (from 11 to 16% to 7–14% of each quadrant), while erosions and fatty lesions increased (from 2 to 33% to 6–28%, and from 4 to 14% to 9–21%, respectively). Sclerosis and ankylosis were infrequent lesions and did not change substantially over time (Table 2).

We found a longitudinal association between the presence of BME in a given quadrant and the presence of sclerosis (OR (95%CI): 1.9 (1.1; 3.4)), erosions (OR:1.9 (1.5; 2.5)) and fatty lesions (OR: 1.9 (1.4; 2.6)) in the same quadrant in the subsequent visit (Table 3). The association between BME and ankylosis was not possible to test, due to the low number of quadrants with ankylosis (n = 36/1536, 2%)). Sensitivity analyses yielded similar findings (Online supplementary Table S2).

The four patterns of BME were distributed in the following order in the 136 patients that had MRI-SIJ available in all visits: no BME (n = 63, 46%), sporadic (n = 34, 25%), fluctuating (n = 21, 15%), and persistent (n = 18, 13%). Patients' baseline characteristics were mostly similar across these BME pattern categories (Table 1). Patients with "persistent BME" were more likely to smoke, when compared with the remaining categories and patients in the "no BME" category were less likely to fulfill the ASAS axSpA criteria, compared to the other groups. Also, patients with 'persistent BME' pattern were more often male, mNY-positive and had a higher mSASSS compared to the other groups.

Compared to patients with 'no BME', patients with the sporadic BME pattern had a higher likelihood of being mNY positive at 5-years (OR (95% CI): 2.1 (1.0; 4.5). Similarly, patients with fluctuating BME (OR: 5.6 (2.2; 14.4), and persistent BME (OR: 7.5 (2.8; 19.6) patterns had a higher likelihood of being mNY positive at 5-years. This relationship reflected a gradient in both the presence of BME and the higher damage associated with it. Similar findings were observed for mNY as a continuous outcome (sporadic (β (95% CI): 0.4 (0.1; 0.8)), fluctuating (β: 1.7 (1.1; 2.3) and persistent (β: 2.3 (1.6; 3.0)) and for ≥5 erosions and/or fatty lesions on MRI-SIJ (sporadic (OR (95% CI): 2.9 (1.4; 5.9)), fluctuating (OR: 4.2 (1.6; 10.8) and persistent (OR: 8.3 (4.1; 16.8)) as outcomes, but not for mSASSS (Table 4). All sensitivity analyses yielded similar findings (Online supplementary Table S3).

Table 3
. Association between BME and structural outcomes on MRI of the SIJs (reference group, No BME), n = 196.

Outcome	Effect of BME (vs no BME) OR [95% CI] [a]
Sclerosis	1.9 (1.1;3.4)
Erosions	1.9 (1.5;2.5)
Fatty lesions	1.9 (1.4;2.6)

When ankylosis was assessed as an outcome, models were not convergent, due to small number of observations. BME: Bone marrow edema; a - Adjusted for symptoms durantions, HLAB27, gender, smoking status, non-steroidal anti-inflammatory drugs (NSAIDs), conventional disease modifying antirheumatic drugs (csDMARDs), biological disease modifying antirheumatic drugs (bDMARDs), and The Ankylosing Spondylitis Disease Activity Score (ASDAS).

Table 4
. Association between SIJ-BME patterns and structural outcomes on radiographs (SIJ and spine) and MRI-SIJ (reference group, No BME).

Imaging outcomes at 5 years	N	Sporadic	Fluctuating	Persistent
mNY (0–8)[a]	124	0.4 (0.1;0.8)	1.7 (1.1;2.3)	2.3 (1.6;3.0)
mNY (yes/no)[b]	124	2.1 (1.0;4.5)	5.6 (2.2;14.4)	7.5 (2.8;19.6)
mSASSS (0–72)[a]	117	−0.2 (−0.9;0.6)	−0.3 (−1.3;0.3)	−0.5 (−1.3;0.3)
≥5 erosions or/and fatty lesions on MRI-SIJ (yes/no) [b]	127	2.9 (1.4;5.9)	4.2 (1.6;10.8)	8.1 (4.1;16.6)
≥3 erosions on MRI-SIJ (yes/no) [b]	127	8.1 (2.4;26.9)	14.7 (3.8;57.3)	10.6 (3.0;37.4)
≥3 fatty lesions on MRI-SIJ (yes/no) [b]	127	7.9 (1.9;31.9)	16.9 (3.9;73.5)	8.0 (1.9;33.9)

BME: bone marrow edema; SIJ: sacroiliac joints; GEE: generalised estimating equations; mNY: modified New York; mSASSS: modified Stoke Ankylosing Spondylitis Spinal Score; MRI: Magnetic resonance imaging.
[a] Estimated by linear GEE.
[b] Estimated by binomial GEE, [c] Estimated by linear regression, All analyses are adjusted for gender, symptom duration, smoking status, human leukotriene antigen-B27, medication and disease activity.

Discussion

We have found that, in patients with early axSpA, there is a longitudinal association between the presence of inflammation and subsequent formation of structural lesions in the same quadrant, i.e., in the same anatomical location, of the SIJ on MRI. In addition, we report an increased risk for the development of structural damage even when inflammatory lesions on the SIJ fluctuate over time, with a dose effect in the association between the exposure to inflammation and the likelihood for structural lesions to occur in the SIJ (both MRI and radiographs).

There was an even distribution of BME and fatty lesions across all quadrants while there was a predominant presence of erosions and sclerosis on the iliac side. These findings are in line with the distribution of elementary lesions found in patients with axSpA [16], such as in a recent Danish study that evaluated the distribution of elementary lesions on MRI across the SIJ of patients with axSpA compared to participants with mechanical back pain [17].

BME decreased over time while structural lesions (erosions and fatty lesions) increased. These findings are concordant with previous studies [9]. In a Dutch study in which the natural history of BME in the SIJ was

Table 2
. Distribution of the different imaging lesions by quadrant.

Baseline (n = 196) and at 5 years (n = 192)										
Left side	BME n(%)		Sclerosis n(%)		Erosions n(%)		Fatty lesion n(%)		Ankylosis n(%)	
	BL	5Y	BL	5Y	BL	5Y	BL	5Y	BL	5Y
Q1	28 (14)	11 (8)	8 (4)	7 (5)	46 (23)	39 (28)	19 (10)	19 (14)	2 (2)	4 (3)
Q2	25 (13)	16 (12)	0 (0)	0 (0)	8 (4)	8 (6)	25 (13)	26 (19)	2 (2)	4 (3)
Q3	23 (12)	9 (7)	0 (0)	0 (0)	3 (2)	4 (3)	15 (8)	25 (18)	3 (2)	4 (3)
Q4	29 (15)	15 (11)	5 (3)	2 (1)	27 (14)	18 (13)	21 (11)	19 (14)	3 (2)	4 (3)
Right side	BME n(%)		Sclerosis n(%)		Erosions n(%)		Fatty lesion n(%)		Ankylosis n(%)	
	BL	5Y	BL	5Y	BL	5Y	BL	5Y	BL	5Y
Q1	27 (14)	16 12)	6 (3)	5 (4)	39 (20)	36 (26)	7 (4)	12 (9)	1 (1)	3 (2)
Q2	27 (14)	19 (14)	0 (0)	0 (0)	12 (6)	10 (7)	28 (14)	29 (21)	1 (1)	3 (2)
Q3	21 (11)	10 (7)	0 (0)	0 (0)	3 (2)	8 (6)	16 (8)	21 (15)	2 (2)	7 (5)
Q4	32 (16)	15 (11)	2 (1)	2 (1)	23 (12)	17 (12)	14 (7)	14 (10)	2 (2)	7 (5)

BME: Bone marrow edema; Q: Quadrant; Q1: upper iliac; Q2: upper sacral; Q3: lower sacral; Q4: lower iliac.

evaluated, after 2 years 47% of the BME lesions present at baseline subsided, with only 8% new BME lesions appearing in the same period.

Similar to previous studies, our findings indicate that current inflammation (BME) in the SIJ leads to future structural lesions (sclerosis, erosions and fatty lesions) [18]. Nevertheless, by using longitudinal autoregressive time-lagged models that allow for a truly longitudinal interpretation of the temporal sequence, we now for the first time have the confirmation that both lesions, inflammatory and subsequent structural lesions, take place in the same anatomical location. This further supports the pathophysiological process underlying the relationship between inflammation and damage. In fact, on average, quadrants with BME were approximately 2 times more likely to show structural lesions in the subsequent visit relative to quadrants without BME in each patient.

We have identified different patterns for the change over time of BME in the SIJ. Of note, in almost half of the patients BME could not be identified over the entire 5 years of follow-up. Only 13% of the patents had persistent BME, while the remaining had either a fluctuating or sporadic pattern. Compared to the remaining groups, those with persistent BME were more likely to smoke, to be male, mNY positive and had also a higher spinal damage (higher mSASSS score). All of these are known factors for radiographic progression at the level of the SIJ in axSpA [19,20].

When assessing the association between BME patterns and future structural damage, there was a dose effect between the presence of BME and structural damage in the SIJ. This pattern reinforces the possible prognostic value of MRI-SIJ for the early assessment of SIJ. Previous studies have shown that structural damage assessed in pelvic radiographs has a low sensitivity to change, while structural lesions (especially fatty lesions) detected on MRI-SIJ are a more sensitive alternative over 5 years in patients with early axSpA [21]. Early detection of inflammatory changes on MRI-SIJ may therefore have relevant clinical and prognostic implications.

This study is not without limitations. As mentioned above the number of patients with structural lesions in the quadrants of the SIJ was rather small, which might influence the effect estimates for our associations of interest. This is however a reflection of our population of patients with early axSpA with still little damage. We have addressed this limitation, to some extent, by using multilevel models that use data from each individual reader separately, an approach we have previously shown to increase the likelihood to detect subtle associations [22]. In addition, we have included patients with axSpA according to the treating rheumatologist which again reflects patients followed in clinical practice. This setting might, however, increase the heterogeneity and again influence our results. Notwithstanding, sensitivity analyses performed in patients with a high level of confidence on the diagnosis and also in patients who also fulfill the ASAS axSpA classification criteria yielded similar results which adds credibility to our findings.

In summary, this study adds to the current knowledge by showing that, in early axSpA, inflammation at the SIJ is associated with subsequent structural damage in the same anatomical location, in a 'dose-response' manner (even when inflammation is fluctuating). These findings strengthen the prognostic significance of bone inflammation in axSpA and shed new light on the mechanisms of this complex disease.

Funding, grant/award info

The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Ethical approval information, institution(s) and number(s)

The DESIR study was conducted according to good clinical practice guidelines and was approved by the appropriate local medical ethical committees (Comité lde Protection des Personnes Ile-de France III). A detailed description of the study protocol is available at the DESIR website (http://www.lacohortedesir.fr/desir-in-english/). The research proposal for this particular analysis was approved by the scientific committee of the DESIR cohort.

Data sharing statement

The data that support the findings of this study was made available by the Scientific Committee of the DESIR cohort (http://www.lacohortedesir.fr/desir-in-english/ and la.cohorte.desir.cch@aphp.fr). Restrictions may apply to the availability of these data used for this study.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

CRediT authorship contribution statement

Santiago Rodrigues-Manica: Visualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Alexandre Sepriano:** Visualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Sofia Ramiro:** Visualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Robert Landewé:** Visualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Pascal Claudepierre:** Visualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Anna Moltó:** Visualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Maxime Dougados:** Visualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Miranda van Lunteren:** Visualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Désirée van der Heijde:** Visualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

None declared.

Acknowledgments

The DESIR study is conducted as a Programme Hospitalier de Recherche Clinique with Assistance Publique Hopitaux de Paris as the sponsor. The DESIR study is also under the umbrella of the French Society of Rheumatology, which financially supports the cohort. An unrestricted grant from Pfizer has been allocated for the first 10 years. The DESIR cohort is conducted under the control of Assistance publique Hopitaux de Paris via the Clinical Research Unit Paris center and under the umbrella of the French Society of Rheumatology and Institut national de la sante et de la recherche medicale (Inserm). Database management is performed within the Department of Epidemiology and Biostatistics (Professeur Jean-Pierre Daures, D.I.M., Nımes, France). We also wish to thank the different regional participating centres: Pr Maxime Dougados (Paris-Cochin B), Pr Andre Kahan (Paris-Cochin A), Pr Philippe Dieudé (Paris-Bichat), Pr Bruno Fautrel (Paris-La Pitie-Salpetriere), Pr Francis Berenbaum (Paris-Saint-Antoine), Pr Pascal Claudepierre (Creteil), Pr Maxime Breban (Boulogne-Billancourt), Dr Bernadette Saint-Marcoux (Aulnay-sous-Bois), Pr Philippe Goupille (Tours), Pr Jean Francis Maillefert (Dijon), Dr Emmanuelle Dernis (Le Mans), Pr Daniel Wendling (Besancon), Pr Bernard Combe (Montpellier), Pr Liana Euller-Ziegler (Nice), Pr Pascal Richette (ParisLariboisiere), Pr Pierre Lafforgue (Marseille), Dr Patrick Boumier (Amiens), Pr Martin Soubrier (ClermontFerrand), Dr Nadia Mehsen (Bordeaux), Pr Damien Loeuille (Nancy), Pr Rene-Marc Flipo (Lille), Pr Alain Saraux (Brest), Pr Xavier Mariette (LeKremlin-Bicetre), Pr Alain Cantagrel (Toulouse), Pr Olivier Vittecoq (Rouen). We wish to thank the research

nurses, the staff members of the Clinical Research Unit of Paris center, the staff members of the Biological Resource Center of Bichat Hospital, the staff members of the Department of Statistics of Nımes and all the investigators, and in particular Jerome Allain, Emmanuelle Dernis, Salah Ferkal, Clement Prati, Marie-Agnes Timsit, Eric Toussirot for active patient recruitment and monitoring. The authors are grateful to Miranda van Lunteren for her work in preparing the database used in this study; and to all DESIR readers without whom this study would not be possible.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2023.152225.

References

[1] Navarro-Compán V, Sepriano A, El-Zorkany B, van der Heijde D. Axial spondyloarthritis. Ann Rheum Dis 2021;80(12):1511–21.
[2] Rudwaleit M, Schwarzlose S, Hilgert ES, Listing J, Braun J, Sieper J. MRI in predicting a major clinical response to anti-tumour necrosis factor treatment in ankylosing spondylitis. Ann Rheum Dis 2008;67(9):1276–81.
[3] Dougados M, Sepriano A, Molto A, van Lunteren M, Ramiro S, de Hooge M, et al. Sacroiliac radiographic progression in recent onset axial spondyloarthritis: the 5-year data of the DESIR cohort. Ann Rheum Dis 2017;76(11):1823–8.
[4] Arnbak B, Jensen TS, Schiøttz-Christensen B, Pedersen SJ, Østergaard M, Weber U, et al. What level of inflammation leads to structural damage in the sacroiliac joints? a four-year magnetic resonance imaging follow-up study of low back pain patients. Arthritis Rheumatol 2019;71(12):2027–33.
[5] Sepriano A, Ramiro S, van der Heijde D, Landewé R. Biological DMARDs and disease modification in axial spondyloarthritis: a review through the lens of causal inference. RMD Open 2021;7(2):e001654.
[6] Torgutalp M, Rios Rodriguez V, Proft F, Protopopov M, Verba M, Rademacher J, et al. Treatment with tumor necrosis factor inhibitors is associated with a time-shifted retardation of radiographic sacroiliitis progression in patients with axial spondyloarthritis: 10-year results from the german spondyloarthritis inception cohort. Arthritis Rheumatol 2022;74(9):1515–23.
[7] Baraliakos X, Listing J, Rudwaleit M, Sieper J, Braun J. The relationship between inflammation and new bone formation in patients with ankylosing spondylitis. Arthritis Res Ther 2008;10(5):104. R.
[8] van der Heijde D, Machado P, Braun J, Hermann KG, Baraliakos X, Hsu B, et al. MRI inflammation at the vertebral unit only marginally predicts new syndesmophyte formation: a multilevel analysis in patients with ankylosing spondylitis. Ann Rheum Dis 2012;71(3):369–73.
[9] van Onna M, van Tubergen A, Jurik AG, van der Heijde D, Landewé R. Natural course of bone marrow oedema on magnetic resonance imaging of the sacroiliac joints in patients with early inflammatory back pain: a 2-year follow-up study. Scand J Rheumatol 2015;44(2):129–34.
[10] Dougados M, Etcheto A, Molto A, Alonso S, Bouvet S, Daures JP, et al. Clinical presentation of patients suffering from recent onset chronic inflammatory back pain suggestive of spondyloarthritis: the DESIR cohort. Joint Bone Spine 2015;82(5):345–51.
[11] Jacquemin C, Rubio Vargas R, van den Berg R, Thevenin F, Lenczner G, Reijnierse M, et al. What is the reliability of non-trained investigators in recognising structural MRI lesions of sacroiliac joints in patients with recent inflammatory back pain? Results of the DESIR cohort. RMD Open 2016;2(2):e000303.
[12] Maksymowych WP, Lambert RG, Østergaard M, Pedersen SJ, Machado PM, Weber U, et al. MRI lesions in the sacroiliac joints of patients with spondyloarthritis: an update of definitions and validation by the ASAS MRI working group. Ann Rheum Dis 2019;78(11):1550–8.
[13] van der Linden S, Valkenburg HA. Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum 1984;27(4):361–8.
[14] Creemers MC, Franssen MJ, van't Hof MA, Gribnau FW, van de Putte LB, van Riel PL. Assessment of outcome in ankylosing spondylitis: an extended radiographic scoring system. Ann Rheum Dis 2005;64(1):127–9.
[15] Machado PM, Landewé R, Heijde DV, (ASAS) AoSiS. Ankylosing Spondylitis Disease Activity Score (ASDAS): 2018 update of the nomenclature for disease activity states. Ann Rheum Dis 2018;77(10):1539–40.
[16] Weber U, Pedersen SJ, Østergaard M, Rufibach K, Lambert RG, Maksymowych WP. Can erosions on MRI of the sacroiliac joints be reliably detected in patients with ankylosing spondylitis? - A cross-sectional study. Arthritis Res Ther 2012;14(3):124. R.
[17] Kiil RM, Mistegaard CE, Loft AG, Zejden A, Hendricks O, Jurik AG. Differences in topographical location of sacroiliac joint MRI lesions in patients with early axial spondyloarthritis and mechanical back pain. Arthritis Res Ther 2022;24(1):75.
[18] Madsen KB, Schiøttz-Christensen B, Jurik AG. Prognostic significance of magnetic resonance imaging changes of the sacroiliac joints in spondyloarthritis–a followup study. J Rheumatol 2010;37(8):1718–27.
[19] Hebeisen M, Micheroli R, Scherer A, Baraliakos X, de Hooge M, van der Heijde D, et al. Spinal radiographic progression in axial spondyloarthritis and the impact of classification as nonradiographic versus radiographic disease: data from the swiss clinical quality management cohort. PLOS One 2020;15(3):e0230268.
[20] Nikiphorou E, Ramiro S, Sepriano A, Ruyssen-Witrand A, Landewé RBM, van der Heijde D. Do smoking and socioeconomic factors influence imaging outcomes in axial spondyloarthritis? Five-year data from the DESIR cohort. Arthritis Rheumatol 2020;72(11):1855–62.
[21] Sepriano A, Ramiro S, van der Heijde D, Dougados M, Claudepierre P, Feydy A, et al. Imaging outcomes for axial spondyloarthritis and sensitivity to change: a five-year analysis of the DESIR cohort. Arthritis Care Res 2022;74(2):251–8. Hoboken.
[22] Sepriano A, Ramiro S, van der Heijde D, Dougados M, Claudepierre P, Feydy A, et al. Integrated longitudinal analysis does not compromise precision and reduces bias in the study of imaging outcomes: a comparative 5-year analysis in the DESIR cohort. Semin Arthritis Rheum 2020;50(6):1394–9.