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What level of inflammation leads to structural damage in the sacroiliac joints?

A 4-year MRI follow-up study of low back pain patients

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ABSTRACT

Objectives: Sacroiliac joint (SIJ) bone marrow oedema (BMO) is considered pivotal in recognition of early spondyloarthritis. However, the link between BMO and development of spondyloarthritis-related bone remodelling remains unclear. We aimed to investigate the evolution of BMO and structural lesions in the SIJs over time.

Methods: Baseline and 4-year follow-up MRI were conducted in 604 patients aged 18-40 years, referred with low back pain to an outpatient spine clinic. Eight SIJ regions were scored for BMO as absent, limited (<25% of subcortical bone region), intermediate (25-50%) or extensive (>50%). Structural lesions including erosions and fat lesions were scored as absent/present.

Results: SIJ BMO was seen at either time point in 41% of participants, but was persistent at both time points in only 16% of participants. Structural SIJ lesions developed according to baseline extent of BMO: baseline limited/intermediate/extensive BMO (as compared with absent) was independently associated with erosion at follow-up with odds ratios (ORs) of 3/5/46 and fat lesion with ORs of 3/7/33, respectively. Of regions with limited and intermediate BMO at baseline 60% and 50% resolved, while only 2% and 7% evolved into extensive BMO at follow-up.

Conclusions: While extensive SIJ BMO was a strong independent predictor for development of structural lesions, limited/intermediate BMO were mostly transient and only rarely evolved into extensive BMO or structural lesions. These findings enhance our understanding of the natural development of SIJ lesions and indicate different progression patterns for limited/intermediate vs. extensive BMO, possibly due to different aetiologies.
Keywords: Low back pain, magnetic resonance imaging, sacroiliac joint, spondyloarthritis.

INTRODUCTION
A broad spectrum of patients with low back pain (LBP) is encountered in clinical practice, the majority of whom present with non-specific LBP. In this heterogeneous population, a small percentage may have axial spondyloarthritis (SpA), and identifying those relatively few patients, specifically those with early SpA, represents a diagnostic challenge.

SpA is a slowly developing disease that may progress to disability and reduced quality of life. The gradual progression of the disease allows, in principle, ample time for early diagnosis and initiation of therapeutic measures that may relieve symptoms and prevent late-stage complications. However, patients with SpA frequently present with symptoms that may resemble non-specific LBP (1), and there are no reliable objective tests that can establish an early diagnosis of SpA with high confidence.

An important step towards identification of early SpA among LBP patients is understanding the natural development of different lesion types in the axial skeleton. Furthermore, it is essential to identify skeletal lesions that are specific to SpA and lesions that are prevalent in non-specific LBP patients, in order to distinguish the two conditions.

Magnetic resonance imaging (MRI) is increasingly used as a diagnostic tool in patients with suspected SpA (2, 3). Specifically, bone marrow oedema (BMO) detected on MRI in the sacroiliac joints (SIJs), is considered pivotal in recognition of early SpA and is incorporated in the Assessment in SpondyloArthritis international Society (ASAS) classification criteria (2). However, the specificity of BMO, particularly that of limited extent, and its relationship to SpA remains a subject of debate (4, 5) because limited BMO is relatively prevalent in patients with non-specific LBP (1, 6, 7) and in healthy individuals (8-10). Accordingly, clinical decisions based on the presence of limited BMO bear a considerable risk of false
positive assignment and potential overtreatment. Structural lesions at the SIJs are also readily detectable on MRI and are considered hallmark signs of manifest SpA, but little is known about the evolution of such lesions over time and their relationship to BMO. Most studies that have investigated the association between MRI findings and SpA have been cross-sectional (11), and the few longitudinal studies in the field have examined highly selected and mostly small samples of SpA patients without inclusion of patients with non-SpA related LBP (12-18).

This study cohort, the Spines of Southern Denmark (SSD), consists of patients with LBP, including an unknown proportion of patients with SpA. The cohort represents the broad spectrum of LBP patients encountered in clinical practice (1). Using repeated MRI scans, we aimed to investigate the temporal and spatial progression of different BMO levels and structural lesions at the SIJs in this non-selected LBP sample.

METHODS

Participants

The participants were recruited from March 2011 to October 2013 from the Spine Centre of Southern Denmark, an outpatient, non-surgical unit specialising in the assessment of patients with back pain within a secondary care public hospital setting. Patients were referred from medical specialists in primary care, chiropractors or from other hospital departments. During the inclusion at baseline, the criteria used to refer patients to the Spine Centre were 1) an episode of back pain of 2 to 12 months’ duration and 2) insufficient clinical response to conservative treatment in primary care. Patients (n=1037) with LBP aged 18-40 years were included at random in the study. Details on the inclusion and exclusion process were reported previously (1). At baseline, all included participants underwent a clinical examination, a blood test, filled in questionnaires and received an MRI of the spine and the SIJs, as detailed
below. All participants were invited by letter to participate in the follow-up project, which ran between November 2014 and June 2017.

Ethical approval was obtained from the Regional Scientific Ethics Committee for Southern Denmark (reference number (S-20140050) and all participants gave their written informed consent. The study was conducted according to the Declaration of Helsinki and Danish legislation.

**Demographic and clinical data**

At baseline, demographic and clinical characteristics, including pain history and activity limitation were collected using patient self-reported questionnaires (1, 19). Baseline data on SpA features were assessed by the consulting clinicians according to a standardised procedure and blood samples were analysed for human leukocyte antigen B27 and high sensitive C-reactive protein (1).

Information on treatment with anti-tumor necrosis factor (anti-TNF) drugs were retrieved from DANBIO, a Danish nationwide clinical register for patients with rheumatological disease, in which registration of all biological treatment is mandatory (20).

**MRI protocol and reading**

The MRI acquisition protocols were published previously (21). In brief, MRI of SIJs was performed with a 1.5 T MRI System (Philips Achieva, Best, The Netherlands). The following sequences were used: Semi-coronal T1-weighted turbo spine echo (TSE) with and without spectral pre-saturation inversion recovery (SPIR), and semi-axial T2-weighted short tau inversion recovery (STIR). Three consultant musculoskeletal radiologists performed the baseline MRI evaluation and two of them (AGJ and AZ) performed the follow-up assessments. All readings were blinded to clinical information except the patient’s age and sex. The follow-up MRI readings were blinded to baseline MRIs. Each MRI was evaluated
by one reader; uncertainties were solved by consensus. The same MRI scanner, MRI protocol and MRI evaluation form were used at both time points.

MRI variables used in the data analyses

The following MRI findings were assessed in the SIJ subcortical bone region: BMO, erosion, fat lesion, sclerosis and ankylosis. The subcortical bone region was defined as the bone parallel to and just beneath the joint surface in the sacrum and iliac bones, respectively. The SIJs on each side were subdivided into four regions: the cartilaginous and ligamentous compartments of the iliac bone and the sacral bone (22). Thus, the subcortical bone region was subdivided into eight regions per patient. The extent of BMO in each region was graded into four levels: absent, limited (<25% of the subcortical bone region), intermediate (25-50% of the subcortical bone region) and extensive (>50% of the subcortical bone region) (22). The minimum criteria for BMO were two lesions on a single slice or one lesion in at least two consecutive slices, in accordance with the ASAS definition of sacroiliitis (23). Other lesion types were assessed as absent or present and also scored according to the minimum criteria described above. Details of the MRI definitions are provided in the supplementary file, Table 1.

Agreement on the MRI evaluations was reported previously (24). Kappa values for inter-observer agreement were .81, .57, .78, and .65 for BMO, erosion, fat lesion and sclerosis, respectively, and kappa values for intra-observer agreement for two readers were .96/.91, .79/.88, .95/.89, and .88/.89, respectively (24).
Statistical analyses

Data analyses were performed using STATA 15.1 (StataCorp, College Station, Tx, USA). Differences at baseline between included and non-included patients were tested using Pearson's Chi Square test and Wilcoxon Rank Sum test, as appropriate. A two-sample proportion test was used to evaluate differences in prevalence between baseline and follow-up.

Associations between baseline BMO and follow-up structural lesions (erosion and fat lesion) were assessed using multivariable logistic regression, adjusted for age, sex and the presence of the given outcome at baseline. To accommodate the potential effect of clustering per patient when conducting regression analyses of multiple SIJ regions, we used the clustered sandwich estimator with patient as the grouping variable to estimate robust standard error (25). The associations are presented as odds ratios (OR) with 95% CI.

RESULTS

Of the 1,037 participants included at baseline, 604 (58%) agreed to participate in the follow-up study. Figure 1 shows the flow chart for the inclusion in the study and reasons for dropout. The median interval between baseline and follow-up MRI scan was 3.8 years (IQR 3.6-4.0). The median age at follow-up was 37 years (IQR 31-41) and 328 (54%) of the follow-up participants were females. Follow-up participants had a slightly higher prevalence of reporting leg pain and pre-baseline episodes of LBP at baseline, and were slightly older compared with non-participants. No other statistically significant differences were found between the two groups (Table 1). Of the participants included in the follow-up study, 12% fulfilled the ASAS criteria for SpA at baseline. However, whether this is a reliable estimate of ‘true’ SpA in this population remains unknown.
MRI findings were relatively frequent and increasing over time in this population, as shown in Table 2. BMO was the most common SIJ finding occurring in 41% at one or both time points, increasing from 23% at baseline to 34% at follow-up (p<0.001, Table 2). Persistent BMO at both time points was seen in 16% of the participants. Of participants with no BMO at baseline, 24% had developed new BMO at follow-up. All new BMO were limited or intermediate.

Evolution of MRI findings at sacroiliac joint region level

Eight SIJ regions were assessed in 604 participants, resulting in a total of 4832 regions. The prevalence of structural lesions in SIJ regions at follow-up increased with the extent of baseline BMO. Among regions with absent, limited, intermediate and extensive BMO at baseline, 1%, 16%, 27%, and 79% had erosion and 4%, 27%, 60%, and 86% had fat lesion at follow-up, respectively (Table 3).

Multiple regression analyses were conducted to assess the association between baseline BMO and structural lesions at follow-up, adjusted for age, sex, and presence of the given structural MRI lesion at baseline. Regional SIJ BMO showed two distinct patterns with baseline extensive BMO, but not baseline limited or intermediate BMO, showing high ORs for prediction of new structural lesions at follow-up. Limited and intermediate BMO at baseline predicted the development of erosion at the same region with ORs of 3.5, and 5.1, respectively, while extensive BMO predicted the development of erosion with an OR of 46.3, corrected for sex, age and presence of erosion at baseline (Table 4). Thus, extensive BMO had approximately 9 times higher odds than intermediate BMO and approximately 13 times higher odds than limited BMO for predicting erosion over 4 years. BMO at baseline also predicted the development of fat lesion at follow-up, where limited, intermediate and extensive BMO showed ORs of 3.2, 6.7 and 32.5, respectively (Table 4). Interestingly, of
regions with absent, limited and intermediate BMO at baseline, only 0%, 2%, and 7%, respectively, developed extensive BMO at follow-up. Furthermore, of regions with limited or intermediate BMO at baseline, 60% and 50%, respectively, disappeared at follow-up (Table 5).

Among the participants, 27 (4%) had been treated with an anti-TNF drug during the follow-up period. To evaluate potential bias from anti-TNF treatment, the analyses shown in Table 4 were re-calculated without these 27 individuals. Exclusion of anti-TNF treated participants did not appreciably affect the results (See supplementary file, Table 2 for details).

**DISCUSSION**

MRI findings in the SIJs, and particularly BMO that is considered an imaging marker of inflammation, are increasingly used to guide diagnosis and treatment in LBP patients with suspected SpA (2-4, 26). However, although MRI may readily visualise SIJ lesions, their natural progression and mutual relationship are poorly understood. In this study, we conducted MRI scans of 604 participants with back pain at time of referral and after 4 years. We found that limited SIJ BMO was relatively prevalent, variable over time and rarely developed into extensive BMO or structural lesions. By contrast, extensive BMO was a strong and independent predictor of the development of new structural lesions. These findings indicate different progression patterns for different levels of BMO, raising the question whether limited vs. extensive BMO may be rooted in different aetiologies. Accordingly, our observations may contribute to guide clinical decisions in the broad patient group with LBP, including those with suspected SpA.
Classification of patients with early SpA

BMO detected by MRI is a cardinal element in the ASAS classification criteria for SpA (2). The ASAS definition of MRI sacroiliitis emphasises the importance of lesions to be ‘highly suggestive of SpA’ and state that caution should be exercised in the interpretation of small BMO lesions (27). However, the condition ‘highly suggestive of SpA’ is not explicitly defined based on objective parameters, and the definition of SIJ BMO by ASAS is consistent with the lower limit used the current study (BMO in more than one slice or two BMO lesions in one slice) (27).

An important observation in the current study is that limited BMO was quite prevalent, variable over time and only rarely developed into extensive BMO or structural lesions. These observations question limited BMO being a cardinal feature of axial SpA. Accordingly, using BMO with the threshold level used in this study and in the ASAS criteria bears a considerable risk of false positive classification and potential overtreatment. This is important if MRI is used as part of the evaluation and selection of candidates for anti-TNF therapy; a concern that has been raised previously (4, 5). The European Medicines Agency mandated MRI to be part of the evaluation of SpA patients that may be candidates for anti-TNF treatment, without imposing a lower threshold for the level of BMO (26). However, there is a need for more accurate definition of the lower threshold for BMO used in classification criteria, to improve the identification of patients with SIJ BMO that is associated with future bone remodelling, e.g. SpA.
The extent of bone marrow oedema as a predictor of structural lesions

We previously reported that low-degree BMO was associated significantly with age but was not associated with any clinical signs of SpA (1). In the current study, we found that different levels of BMO showed different courses of development during the follow-up period. Extensive BMO at baseline was a strong independent predictor of structural lesions at follow-up showing ORs of 33 for the development of new fat lesion and 46 for the development of new erosion. By contrast, limited and intermediate baseline BMO predicted relatively weakly the development of structural lesions (ORs <7). In addition, low-grade BMO was relatively variable over time and frequently reversible. Limited and intermediate BMO at baseline were resolved in over half of regions at follow-up, and developed into extensive BMO in only 2% and 7%, respectively (Table 5). Collectively, these different paths of progression suggest that low levels of oedema may often be transient in nature with limited effect on bone morphology, while extensive oedema may be more likely rooted in pathology that leads to structural lesions at the SIJs.

Since structural damage is a hallmark sign of fulminant late-stage SpA, extensive BMO seems more likely to be associated with SpA, while low BMO levels may be more reflective of axial stress or degenerative changes (1). Previous studies investigating possible non-SpA related causes of SIJ BMO are sparse, but a number of factors have been suggested to associate with BMO, including pregnancy/birth-related stress, obesity, extensive physical activity and age-related degeneration (5, 8, 10, 28-30). In a study by Weber et al. investigating physically active healthy young individuals, the authors found that, when present, BMO was primarily seen at low levels and clustering topographically in distinct SIJ regions (8). Similar results were observed by de Winter et al in LBP patients, in runners and in other healthy controls (9). Interestingly, de Winter et al also found that BMO occurring throughout the SIJs and deep lesions (≥1 cm depth) were predominantly seen in SpA patient
(9). The observations from these studies (8, 9) together with our observations may support the notion that local BMO could be stress-related, possibly affecting specific local “load-areas” at the SIJs, while BMO related to a systemic disease, may cover a more extensive area and lead to structural lesions.

Only few previous longitudinal studies have included data on the severity level of BMO. In an 8-year follow-up study, Bennett et al investigated 40 patients, all diagnosed with SpA, and examined the link between baseline BMO and ankylosing spondylitis at follow-up (12). The diagnosis of ankylosing spondylitis at follow-up was based on clinical symptoms and pelvic radiography. In these SpA patients, the authors found that a composite variable of positive HLA-B27 tissue type and severe baseline SIJ BMO predicted the diagnosis of ankylosing spondylitis with a likelihood ratio of 8. Madsen et al. investigated 94 patients with a diagnosis of SpA, with repeated MRI scans and a follow-up time varying between 2 and 8 years (13). They found a positive association between a compiled score based on baseline BMO and a composite score for structural changes (erosion, fat lesion and ankylosis combined) at follow-up (13). However, these studies were not aimed at investigating the temporal and spatial connection between regional SIJ lesions, i.e. whether BMO in a localised region preceded structural changes, including erosion, at that same region. Thus, the reported correlations were not conducted at regional level and were not adjusted for pre-existing structural lesions at baseline to demonstrate emergence of new structural lesions at follow-up.

In the current study we identified distinct progression patterns for BMO based on its extent. Importantly, the role of extensive BMO as a strong and independent predictor of future emergence of structural lesions has not been established previously, to our knowledge. The facts that 1) BMO is a marker of inflammation, 2) extensive BMO precedes development of new structural lesions, specifically erosions, and 3) new erosions appear in regions of
previous extensive BMO provide support for the hypothesis that inflammation, particularly at high levels, may be part of the pathogenesis underlying SIJ bone remodelling.

**Strengths and limitations**

A methodological strength of the current study is the examination of an unselected population of patients with LBP reflecting the heterogeneous spectrum of patients encountered in clinical practice, and allowing to observe the progression of different levels of BMO that may be rooted in different aetiology. Furthermore, the large number of participants strengthens the precision of the estimated prevalence rates and associations.

One study limitation was that MRI scans were only evaluated by one reader, and possible uncertainty in MRI scoring may have been alleviated by using multiple readers. Furthermore, while the follow-up period of 4 years may be sufficient to observe the evolution of some MRI findings in LBP patients, SpA is a slowly developing disease, and thus, studies of even longer time spans are needed to fully clarify the evolution of lesions, including BMO and structural changes in the longer term.

**Conclusion**

We have shown that in a non-selected sample of patients with LBP, low degree BMO was relatively prevalent, mostly transient and only rarely developed into extensive BMO or structural lesions. By contrast, extensive BMO strongly predicted the development of new structural lesions in the same region. These observations raise the hypothesis of potential different progression patterns for limited/intermediate vs. extensive BMO, possibly due to different aetiologies. While low levels of oedema may often be temporary in nature with limited effect on bone morphology, extensive oedema may more likely represent pathology that leads to structural lesions at the SIJs, possibly associated with SpA. Our findings call for
a re-appraisal of low-level BMO in the classification of LBP patients. In addition, these results provide insight into the natural progression of SIJ lesions and may facilitate the development and improvement of tools aimed at identifying patients with early SpA.

ACKNOWLEDGEMENT

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AUTHOR CONTRIBUTIONS

All authors contributed to the concept and design of the study. AGJ and AZ performed the reading of the MRI evaluations. BA performed the interpretation and analyses of the data and drafted the manuscript. All authors critically revised and approved the final version to be submitted for publication.

Figure 1. Flow chart of inclusions in the follow-up study from the Spines of Southern Denmark (SSD) cohort.
### Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Participants</th>
<th>Non-participants</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>(IQR)</td>
</tr>
<tr>
<td>Age in years a</td>
<td>33 *</td>
<td>(27-37)</td>
</tr>
<tr>
<td>LBP duration in months b</td>
<td>10</td>
<td>(4-36)</td>
</tr>
<tr>
<td>LBP intensity (0-10) b</td>
<td>6</td>
<td>(5-7)</td>
</tr>
<tr>
<td>Activity limitation (RMDQ 0-100) b</td>
<td>57</td>
<td>(39-74)</td>
</tr>
<tr>
<td>Women a</td>
<td>54</td>
<td>(50-58)</td>
</tr>
<tr>
<td>Sick leave due to back pain in the last 3 months c</td>
<td>50</td>
<td>(45-54)</td>
</tr>
<tr>
<td>Employed b</td>
<td>73</td>
<td>(69-76)</td>
</tr>
<tr>
<td>Previous LBP episode(s) b</td>
<td>77 *</td>
<td>(74-81)</td>
</tr>
<tr>
<td>Leg pain</td>
<td>78 *</td>
<td>(74-82)</td>
</tr>
<tr>
<td>HLA-B27 positive a</td>
<td>11</td>
<td>(9-14)</td>
</tr>
<tr>
<td>Elevated hsCRP a</td>
<td>8</td>
<td>(6-10)</td>
</tr>
<tr>
<td>Peripheral arthritis a</td>
<td>2</td>
<td>(1-4)</td>
</tr>
<tr>
<td>Heel enthesitis a</td>
<td>3</td>
<td>(2-4)</td>
</tr>
<tr>
<td>Uveitis a</td>
<td>1</td>
<td>(0-2)</td>
</tr>
<tr>
<td>Dactylitis a</td>
<td>1</td>
<td>(0-2)</td>
</tr>
<tr>
<td>Psoriasis a</td>
<td>6</td>
<td>(4-8)</td>
</tr>
<tr>
<td>Inflammatory bowel disease a</td>
<td>1</td>
<td>(0-2)</td>
</tr>
<tr>
<td>Family disposition a</td>
<td>18</td>
<td>(15-22)</td>
</tr>
<tr>
<td>Good response to NSAID a</td>
<td>14</td>
<td>(11-17)</td>
</tr>
<tr>
<td>Inflammatory back pain according to ASAS a</td>
<td>18</td>
<td>(15-21)</td>
</tr>
<tr>
<td>Sacroiliitis according to ASAS a</td>
<td>23</td>
<td>(19-26)</td>
</tr>
<tr>
<td>Fulfilment of the ASAS criteria</td>
<td>12</td>
<td>(9-14)</td>
</tr>
</tbody>
</table>

*p-value < 0.05 for difference between participants and non-participants in the follow-up study. The number of follow-up participants was 604 and the number of non-participants was 433, some variables had missing values, a: <3% missing values, b: 5-8% missing values, c: 13% missing values.

IQR: inter quartile range, LBP: low back pain, (LBP intensity is averaged 0–10 Numerical Rating Scales on present LBP, worst LBP last 14 days and typical LBP last 14 days), RMDQ: Roland Morris Disability Questionnaire (calculated as a proportional score), HLA: human leukocyte antigen, hsCRP: high sensitive C-reactive protein (known causes for elevated hsCRP excluded), NSAID: non-steroid anti-inflammatory drug, ASAS: Assessment in SpondyloArthritis international Society
Table 2. Prevalence of MRI findings at baseline and follow-up

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Follow-up</th>
<th>Any time point</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td><strong>Per patient (n= 604)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One or more lesion type</td>
<td>173 (29)</td>
<td>267 (44)</td>
<td>297 (49)</td>
</tr>
<tr>
<td>BMO</td>
<td>137 (23)</td>
<td>205 (34)</td>
<td>248 (41)</td>
</tr>
<tr>
<td>Erosion</td>
<td>50 (8)</td>
<td>67 (11)</td>
<td>82 (14)</td>
</tr>
<tr>
<td>Fat lesion</td>
<td>87 (14)</td>
<td>119 (20)</td>
<td>141 (23)</td>
</tr>
<tr>
<td>Sclerosis</td>
<td>50 (8)</td>
<td>47 (8)</td>
<td>70 (12)</td>
</tr>
<tr>
<td>Ankylosis</td>
<td>0 (0)</td>
<td>3 (1)</td>
<td>3 (1)</td>
</tr>
<tr>
<td><strong>Per region (n=4832)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One or more lesion type</td>
<td>480 (10)*</td>
<td>568 (12)</td>
<td>738 (15)</td>
</tr>
<tr>
<td>BMO</td>
<td>295 (6)</td>
<td>357 (7)</td>
<td>522 (11)</td>
</tr>
<tr>
<td>Erosion</td>
<td>112 (2)</td>
<td>136 (3)</td>
<td>177 (4)</td>
</tr>
<tr>
<td>Fat lesion</td>
<td>260 (5)</td>
<td>273 (6)</td>
<td>383 (8)</td>
</tr>
<tr>
<td>Sclerosis</td>
<td>81 (2)</td>
<td>74 (2)</td>
<td>119 (2)</td>
</tr>
<tr>
<td>Ankylosis</td>
<td>0 (0)</td>
<td>6 (0)</td>
<td>6 (0)</td>
</tr>
</tbody>
</table>

* p-value < 0.05 for difference between baseline and follow-up.
BMO: bone marrow oedema

Table 3. Evolution of follow-up erosions and fat lesions in relation to baseline bone marrow oedema at region level.

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Follow-up</th>
<th>Erosion</th>
<th>Fat lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td><strong>Absent BMO</strong></td>
<td>4537</td>
<td>67 (1)</td>
<td>167 (4)</td>
</tr>
<tr>
<td><strong>Limited BMO</strong></td>
<td>236</td>
<td>38 (16)</td>
<td>63 (27)</td>
</tr>
<tr>
<td><strong>Intermediate BMO</strong></td>
<td>30</td>
<td>8 (27)</td>
<td>18 (60)</td>
</tr>
<tr>
<td><strong>Extensive BMO</strong></td>
<td>29</td>
<td>23 (79)</td>
<td>25 (86)</td>
</tr>
</tbody>
</table>

n Total= 4832, BMO: bone marrow oedema
Limited: <25% of the subcortical bone region, Intermediate: 25-50% of the subcortical bone region, Extensive: >50% of the subcortical bone region

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Table 4. Multivariable analysis of the association between baseline bone marrow oedema and structural lesions at 4-year follow-up.

<table>
<thead>
<tr>
<th>Baseline (predictors)</th>
<th>Follow-up (outcome)</th>
<th>Erosion a</th>
<th>Fat lesion b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>CI</td>
<td>OR</td>
</tr>
<tr>
<td><strong>Limited BMO</strong></td>
<td>3.5</td>
<td>1.6-7.4</td>
<td>3.2</td>
</tr>
<tr>
<td><strong>Intermediate BMO</strong></td>
<td>5.1</td>
<td>1.2-21.7</td>
<td>6.7</td>
</tr>
<tr>
<td><strong>Extensive BMO</strong></td>
<td>46.3</td>
<td>12.8-166.8</td>
<td>32.5</td>
</tr>
</tbody>
</table>

Regions with absent BMO at baseline were used as reference in the logistic regression analysis. Bold font indicates significant ORs (p<0.05). \( n_{total} = 4832 \).

a: Model adjusted for age, sex and the presence of erosion at baseline.
b: Model adjusted for age, sex and the presence of fat lesion at baseline.

OR: odds ratios, CI: 95% confidence interval, BMO: bone marrow oedema

**Limited:** <25% of the subcortical bone region, **Intermediate:** 25-50% of the subcortical bone region, **Extensive:** >50% of the subcortical bone region.

Table 5. Evolution of extent of bone marrow oedema at the sacroiliac joint over 4 years.

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Absent</th>
<th>Limited</th>
<th>Intermediate</th>
<th>Extensive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td><strong>Absent</strong></td>
<td>4537</td>
<td>4310 (95)</td>
<td>217 (5)</td>
<td>10 (0)</td>
</tr>
<tr>
<td><strong>Limited</strong></td>
<td>236</td>
<td>141 (60)</td>
<td>81 (34)</td>
<td>10 (4)</td>
</tr>
<tr>
<td><strong>Intermediate</strong></td>
<td>30</td>
<td>15 (50)</td>
<td>8 (27)</td>
<td>5 (17)</td>
</tr>
<tr>
<td><strong>Extensive</strong></td>
<td>29</td>
<td>9 (31)</td>
<td>11 (38)</td>
<td>5 (17)</td>
</tr>
</tbody>
</table>

Some rows may not add up to 100% due to rounding. \( n_{total} = 4832 \)

**Limited:** <25% of the subcortical bone region, **Intermediate:** 25-50% of the subcortical bone region, **Extensive:** >50% of the subcortical bone region.
Reference list


Initially allocated to the study, n=1619

Reasons for exclusion before the first consultation:
- Patient non-attendance, n=60
- Attended clinician outside the study, n=100

Patients attending first consultation, n=1459

Reasons for exclusion after the first consultation:
- Declined participation, n=94
- Less than 18 years or more than 40 years, n=12
- Did not understand Danish, n=10
- Primary complaint not LBP, n=37
- MRI within last year, n=64
- Contraindications for MRI, n=78
- Deemed unlikely to tolerate one-hour MRI, n=40
- Incomplete MRI due to logistic or technical difficulties, n=68
- Patient non-attendance to MRI, n=19

Included in the SSD cohort at baseline, n=1037

Missing contact information, n=29

Invited to participate in follow-up, n=1008

Reason for exclusion:
- Non-responders/ did not wish to participate, n=353
- Non attendance, n=30
- Contraindications, n=21

Included in the follow-up study, n=604