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Original article

Associations between syndesmophytes and facet joint ankylosis in radiographic axial spondyloarthritis patients on low-dose CT over 2 years

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Abstract

Objectives. In radiographic axial spondyloarthritis (r-axSpA), spinal damage manifests as syndesmophytes and facet joint ankylosis (FJA). We evaluated whether the presence of one lesion increased the risk of the other lesion.
Methods. Patients with r-axSpA underwent low-dose CT (ldCT) and MRI of the whole spine at baseline and 2 years. On ldCT, vertebrae were scored for presence and size of syndesmophytes; facet joints were assessed for ankylosis. MR images were assessed for inflammation. Two hypotheses were tested: (i) presence of FJA is associated with new syndesmophyte(s) on the same vertebral unit (VU) 2 years later, and (ii) presence of bridging syndesmophyte(s) is associated with new FJA on the same VU 2 years later. Two generalized estimating equations models were tested per hypothesis using increase of FJA/syndesmophytes (model A) or presence of FJA/syndesmophytes (model B) as outcome, adjusted for inflammation at baseline. Secondary analyses tested the hypotheses with outcomes on adjacent VUs and dose–response effects.
Results. Fifty-one patients were included (mean age 49, 84% male, 82% HLA-B27$^+$). Baseline bridging syndesmophytes occurred more often (range: 10–60% per VU) than FJA (range: 8–36%). Odds ratios (ORs) (95% CI) for presence of bridging syndesmophytes on development of FJA were 3.55 (2.03, 6.21) for model A and 3.30 (2.14, 5.09) for model B. ORs for presence of baseline FJA on new syndesmophytes were 1.87 (1.20, 2.92) for model A and 1.69 (0.88, 3.22) for model B. Secondary analyses yielded positive ORs for both hypotheses.
Conclusions. Bone formation in vertebrae and in facet joints influence each other's occurrence, with the effect of syndesmophytes being larger than that of FJA.

Key words: radiographic axial spondyloarthritis, syndesmophytes, facet joints, ankylosis, low dose CT

Rheumatology key messages

- Bridging syndesmophytes increase risk of facet joint ankylosis in the same and adjacent vertebral units.
- Facet joint ankylosis increases risk of syndesmophytes in the same and adjacent vertebral units.
- Inflammation in posterior elements was positively associated with facet joint ankylosis 2 years later.

Introduction

Radiographic axial spondyloarthritis (r-axSpA) is characterized by inflammation and structural damage in the sacroiliac joints and, in a subset of patients, the spine [1]. Spinal lesions can occur in several locations, including the vertebrae, facet joints and ligaments [2]. Syndesmophytes are osseous spikes on the vertebral rim, being formed from ossification of the annulus fibrosis, anterior longitudinal ligament and paravertebral

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CLINICAL SCIENCE

connective tissue, and growing in the direction of the adjacent vertebra [3]. Fusion of two vertebrae occurs when a syndesmophyte has crossed the intervertebral disc space and formed a so-called bridging syndesmophyte to the adjacent vertebra [4]. Pathological bone formation has also been shown to occur in the facet joints [also known as (zyg)apophyseal joints], causing facet joint ankylosis (FJA) [5, 6]. There are conflicting data on the direction of the association between FJA and (bridging) syndesmophytes. One study reported that bridging syndesmophytes occur infrequently without FJA, hence proposing that facet joints are primarily involved in r-axSpA [7]. Another study reported that FJA was more strongly associated with bridging than non-bridging syndesmophytes and that thoracolumbar syndesmophytes occurred often without FJA, therefore suggesting that syndesmophyte development precedes FJA [8].

Several techniques have been used over the years to study structural lesions in the spine, with lateral cervical and lumbar conventional radiography (CR) being the most widely used technique [9–12]. In recent years, low dose CT (ldCT) has been shown to be an adequate and feasible technique for repeated imaging of the whole spine [13, 14]. Its ability to capture the thoracic spine gives it certain superiority over CR as an imaging tool, especially since syndesmophytes have been reported to occur and progress most in the thoracic spine [9, 15]. Furthermore, its drastically lowered radiation dose relative to conventional CT makes it a feasible technique to apply repeatedly to the whole spine.

Multiple studies have looked into factors associated with syndesmophyte development. Associations have been made with factors including disease activity, disease duration, smoking, age, gender and presence of existing syndesmophytes, the latter being the most prominent and frequently confirmed contributing factor [16]. Other studies, looking more into the pathophysiological process, found significant effects of vertebral corner inflammation and vertebral corner fat deposition on the development of syndesmophytes [17, 18]. Since we know that presence of existing syndesmophytes is a predictor for further syndesmophyte development, the question arises whether this is due to the rigidity that is caused by the syndesmophytes, and perhaps rigidity elsewhere in the spinal column. In the current study we hypothesize a mechanical effect of rigidity in the spine resulting in bone formation, looking specifically at the interplay between FJA and syndesmophytes in the same area of the spine. Using whole spine ldCT we study whether presence of bridging syndesmophytes increases the risk of FJA, and whether presence of FJA increases the risk of syndesmophyte formation at the same or adjacent vertebral level.

Methods

Patients

Data were used from the Sensitive Imaging in Ankylosing Spondylitis (SIAS) cohort, which included r-axSpA patients from Leiden, the Netherlands, and Herne, Germany. The study was approved by the medical ethical committees of Leiden (Medisch Ethische Toetsings Commissie, P10.021) and Herne (Ethikkommission der Rurh Universität Bochum, 4366-12). Patients fulfilled the modified New York criteria, had at least one inflammatory lesion on spinal MRI and between one and 18 syndesmophytes on lateral cervical and lumbar CR. All patients gave written informed consent.

Imaging techniques

ldCT and MR images of the whole spine were collected at baseline and 2 years. MR images with 3.5 mm sagittal slices were obtained on a 3 T (Leiden) and 1.5 T scanner (Leiden: Philips Medical Systems, Best, The Netherlands; Herne: Siemens Aera 1.5, Siemens, Erlangen, Germany). ldCT images with 1 mm axial slices and 2 mm sagittal and coronal slices were obtained on a 64-section (Leiden) and 16-section CT scanner (Leiden: Aquilion 64, Toshiba Medical Systems, Otawara, Japan; Herne: Somatom Emotion 16, Siemens).

ldCT scoring methods and variable definitions

ldCT images were assessed for presence and size of syndesmophytes on sagittal and coronal slices with the Computed Tomography Syndesmophyte Score (CTSS) and for presence of FJA on axial slices by two trained, central readers. The CTSS has been described in detail in a separate publication [14]. In short, the CTSS assesses four quadrants of a vertebral unit (VU) per plane. A VU comprises the lower half of a vertebra, the upper half of the vertebra underneath and the intervertebral disc space (IDS) in between (Supplementary Fig. S1, available at *Rheumatology* online). Scores use a four-point scale per quadrant: 0: no syndesmophyte; 1: syndesmophyte reaching $<$50% of the IDS; 2: syndesmophyte reaching $\geq$50% of the IDS; 3: syndesmophyte bridging the IDS. Thus, a maximum of eight syndesmophytes or four bridging syndesmophytes can be scored with the CTSS per VU. For both syndesmophyte and FJA scoring, the readers could attribute a missing score if the location was difficult to assess due to, for example, image quality.

Dichotomous status scores at baseline and follow-up were made per reader, per VU, to show whether there was presence of at least one (out of eight) syndesmophyte. Furthermore, a change score was made per VU, per reader, reflecting whether there was an increase in the number of syndesmophytes over time. The change score was set to missing if all non-missing quadrants in a VU had a syndesmophyte at baseline and thus could not show change over time. A status score at baseline was made to show whether there was presence of at least one bridging syndesmophyte in the VU. Lastly, a status score at baseline was made showing how many quadrants of the VU had a bridging syndesmophyte (range 0–4). Presence of FJA was coded dichotomously per reader for the left and right facet joint. For FJA,

similar variables were made as described above. Dichotomous, individual reader status scores at baseline and follow-up showed whether there was presence of at least one (out of two) ankylosed facet joint per VU. A change score showed whether there was an increase in the number of ankylosed facet joints over time, and this was set to missing if all facet joints with non-missing scores in a VU were ankylosed at baseline. Lastly, a status score at baseline was made showing how many facet joints were ankylosed (range 0–2).

MRI scoring methods and variable definitions

Bone marrow oedema suggestive of spondyloarthritis was scored by three trained central readers on short-tau inversion recovery images. Inflammation on the vertebral bodies was scored with the Spondyloarthritis Research Consortium of Canada (SPARCC) scoring system and coded as inflammation present or absent per VU based on agreement by $\geq$2/3 readers [19]. Inflammation in the posterior elements (pedicles and soft tissue in C2–T1; facet joints, processes, pedicles and soft tissues in T1–S1) was also coded as present or absent per VU if inflammation was present in at least one of the posterior elements according to $\geq$2/3 readers.

Statistical analyses

To test whether there is a longitudinal relationship between syndesmophytes and FJA, two hypotheses were formulated, looking at both directions—hypothesis 1: presence of FJA is associated with a new syndesmophyte on the same VU 2 years later; and hypothesis 2: presence of a bridging syndesmophyte is associated with new FJA on the same VU 2 years later. We used multivariable multilevel generalized estimating equation (GEE) models to assess the hypotheses at the VU-level and to use scores from each individual reader, which increases statistical power [20]. Because the models take into account correlations within patients (the correlation between VUs from the same patient) next to the change in VUs on different time points, the effects should be interpreted as truly longitudinal. An exchangeable working correlation structure was used to handle the VU-level.

Each hypothesis was tested in two types of models. Model A ('change-score' model) looked at the effect of the predictor at baseline on the increase in the number of lesions at follow-up. For example, for hypothesis 1, model A studied the effect of the presence of FJA at baseline on the syndesmophyte change score ($\geq$1 new syndesmophyte). Model B ('autoregressive' model) looked at the effect of the predictor at baseline on the presence of a lesion in a VU at follow-up adjusting for its presence at baseline (the 'autoregressor'). For example, for hypothesis 2, model B studied the effect of a bridged syndesmophyte at baseline on presence of $\geq$1 ankylosed facet joint in a VU at follow-up (status score), adjusted for the presence of $\geq$1 ankylosed facet joint in the VU at baseline. All models were adjusted for the presence of inflammation at baseline on the location of the outcome, e.g. presence of inflammation at baseline on the vertebral body for hypothesis 1 and presence of inflammation in the posterior elements at baseline for hypothesis 2.

Additional analyses were performed (using also models A and B) to (i) assess the hypotheses on adjacent VUs, and (ii) assess a dose–response effect between the bony lesions. For additional analyses (i), associations were tested between the predictor on one VU and the outcome on the VU above, the VU below, two VUs above and two VUs below (see Supplementary Fig. S2, available at *Rheumatology* online). The models were again adjusted for inflammation at baseline on the location of the outcome. For additional analyses (ii), the same models as for the primary analyses were used, but now replacing the binary predictor (for FJA present/absent at baseline and bridging syndesmophyte(s) present/absent at baseline) with the categorical predictor (ankylosis in 0, 1 or 2 facet joints and bridging syndesmophytes in 0, 1, 2, 3 or 4 quadrants). These models are used to assess presence of a dose–response effect, i.e. does the risk of developing the outcome increase if there is greater presence of the predictor? All previously mentioned analyses were performed on a group level. To assess the relationship between the presence of bridging syndesmophytes and FJA on a patient level a cumulative probability plot was made of the average reader scores per patient of the number of VUs with at least one bridging syndesmophyte and the number of VUs with at least one ankylosed facet joint. This figure is used to assess the frequency of occurrence of both lesions within each patient, to see which occurs more often.

Intraclass correlations coefficients (ICCs) for syndesmophyte scores and FJA scores were previously published [6, 14]. The ICC for inflammation in the posterior elements was calculated on the patient level for baseline status scores using two-way mixed effect average ICCs, and was 0.82. The ICC for inflammation on the vertebral bodies at baseline, with the same model, was 0.89.

Previously, the ability of ldCT to assess FJA was evaluated, and VUs from C5–C6 until T1–T2 were deemed difficult to assess [6]. Therefore, facet joint scores from these four VUs were excluded from all analyses.

Patient and public involvement

There is structural patient participation in all research projects at the Leiden University Medical Center's Department of Rheumatology. This is achieved through a patient council. The current study is in line with the council's wish to prevent development and progression of structural damage in r-axSpA. Patients were not directly involved in designing or conducting the study, but patient(s) were part of the medical ethical committee for both centres.

Results

ldCT scans at baseline and 2 years and MRI scans at baseline from 51 patients were included in the analyses

Fig. 1 Occurrences of bridging syndesmophytes and facet joint ankylosis at baseline

VU	Segment	≥1 bridging syndesmophyte at BL		≥1 FJA at BL	
		Reader 1	Reader 2	Reader 1	Reader 2
1	Cervical	22%	27%	12%	34%
2		25%	25%	14%	21%
3		25%	29%	23%	20%
4		33%	34%	NA	NA
5		20%	29%	NA	NA
6		25%	23%	NA	NA
7	Thoracic	27%	31%	NA	NA
8		33%	39%	23%	28%
9		49%	47%	27%	33%
10		55%	59%	26%	37%
11		45%	55%	22%	35%
12		47%	47%	26%	29%
13		57%	57%	29%	29%
14		55%	57%	24%	31%
15		49%	55%	24%	33%
16		55%	59%	25%	37%
17		53%	49%	27%	29%
18		48%	48%	28%	36%
19	Lumbar	26%	28%	16%	24%
20		28%	24%	12%	22%
21		22%	22%	12%	14%
22		20%	22%	10%	20%
23		12%	12%	10%	12%

Numbers represent the percentage of patients with the event (all coded binary), per vertebral unit, per reader. Maximum number of total patients per cell is 51 patients; numbers can be lower due to missing scores. Facet joint ankylosis scores at vertebral units 4–7 are excluded due to poor visibility. VU1: C2–C3; VU23: L5–S1. BL: baseline; FJA: facet joint ankylosis; NA: not applicable; VU: vertebral unit.

(mean age 49 years (S.D. 10), 68% male, 78% HLA-B27$^+$) (Supplementary Table S1, available at *Rheumatology* online). The occurrence of inflammation is presented in Supplementary Fig. S2, available at *Rheumatology* online. The presence of bridging syndesmophytes and FJA at baseline per reader per VU is presented in Fig. 1. Both FJA and bridging syndesmophytes are present at baseline in every VU in at least one patient. Both lesions occur more often in the thoracic spine; bridging syndesmophytes occur more often than FJA at essentially all levels. Figure 2 presents this data on the patient level, showing that in the vast majority of patients, the number of VUs with bridging syndesmophytes exceeds the number of VUs with FJA.

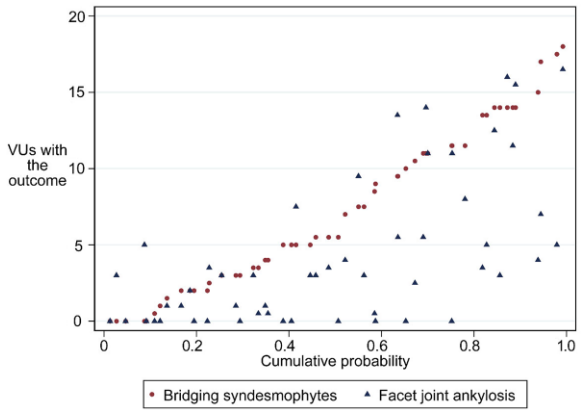
Per patient, 23 VUs were imaged per time point, yielding a total of 1173 VUs to be assessed over time. After excluding FJA scores for C5–C6 until T1–T2, missing scores for ldCT images due to, for example, poor visibility were low, ranging from 0.5% to 2% for CTSS and 1.9% to 4.4% for FJA scores on baseline and follow-up for both readers. VUs with missing scores were not imputed and were excluded from analyses.

For reader 1, 999 VUs had no syndesmophytes at baseline ($n = 451$), or had a syndesmophyte on ≥ 1 but not all quadrants of the VU ($n = 548$). Of these, 16% (164/999) developed a syndesmophyte after 2 years. Of the 451 VUs that had no syndesmophyte at baseline, 10% (44/451) developed a syndesmophyte. Reader 2 reported similar results with 18% (186/1008) and 11% (45/410). For reader 1, 750 VUs had zero ($n = 728$) or one ($n = 22$) ankylosed facet joint at baseline. Of these, 5% (41/750) of VUs developed FJA after 2 years. Of the 728 VUs without FJA at baseline, 5% (36/728) developed FJA. Reader 2 reported similar results of 7% (52/718) and 6% (42/680).

Main model results

Results for the main analyses are presented in Table 1. Odds ratios (ORs) for the association between FJA at baseline and syndesmophyte development at follow-up (hypothesis 1) were 1.87 (1.20, 2.92) for the increase in the number of syndesmophytes (model A), and 1.69 (0.88, 3.22) for VUs with new presence of syndesmophytes (model B). In both models, vertebral body inflammation at baseline was significantly associated with the outcome. ORs for the association between bridging syndesmophytes at baseline and FJA development at follow-up (hypothesis 2) were slightly higher and significant for both models, with 3.55 (2.03, 6.21) for model A

Fig. 2 Presence of bridging syndesmophytes and facet joint ankylosis at baseline on the patient level



The figure shows the presence of bridging syndesmophytes and facet joint ankylosis at baseline in each individual patient. The plot is ordered by increasing number of VUs with bridging syndesmophytes, and information on syndesmophytes and facet joint ankylosis is linked per patient (e.g. patient at the 0.4 probability of syndesmophytes has five bridging syndesmophytes and no ankylosed facet joints). Scores are the mean of both readers of the number of vertebral units with at least one bridging syndesmophyte and the number of vertebral units with at least one ankylosed facet joint. The range for both scores is 0–19. VU, vertebral unit.

and 3.30 (2.14, 5.09) for model B. In these models, the association between inflammation in the posterior elements at baseline was only significant for model B.

Additional model results

Results for the analyses on adjacent VUs are presented in Table 2. For hypothesis 1, statistically significant ORs for the association between FJA at baseline and syndesmophyte development at follow-up were found on one VU above or below and two VUs below. For hypothesis 2, significant ORs for the association between bridging syndesmophytes at baseline and FJA development at follow-up were also found for one VU above or below and two VUs below.

Results for the analyses assessing presence of a possible dose–response effect are presented in Table 3. For all models there is an upward trend where the ORs become larger when there is greater presence of the predictor. For models including FJA as a predictor effects remain small, the greatest being the effect of having two ankylosed facet joints on the increase of syndesmophytes [2.15 (1.24, 3.27)]. For models including bridging syndesmophytes as a predictor the effects increase drastically: having one quadrant (compared with zero quadrants) with a bridged syndesmophyte yields an OR of 2.22 (0.90, 5.46) for the increase of FJA and 2.35 (1.27, 4.34) for the presence of FJA, while having four quadrants with bridged syndesmophytes (compared with zero quadrants) yields an OR of 6.43 (2.95, 14.03)

Table 1 Multivariable models association between FJA and syndesmophyte development 2 years later and bridging syndesmophytes and the development of FJA 2 years later

Models	OR (95% CI) ($n = 51$)
Effect of FJA on increase syndesmophytes (hypothesis 1A)	
Baseline FJA	**1.87 (1.20, 2.92)**
Baseline vertebral body inflammation	**1.88 (1.28, 2.76)**
Effect of FJA on presence syndesmophytes (hypothesis 1B)	
Baseline FJA	1.69 (0.88, 3.22)
Baseline vertebral body inflammation	**2.32 (1.40, 3.85)**
Effect of bridging syndesmophytes on increase FJA (hypothesis 2A)	
Baseline bridging syndesmophyte	**3.55 (2.03, 6.21)**
Baseline posterior elements inflammation	2.21 (0.73, 6.65)
Effect of bridging syndesmophytes on presence FJA (hypothesis 2B)	
Baseline bridging syndesmophyte	**3.30 (2.14, 5.09)**
Baseline posterior elements inflammation	**2.49 (1.20, 5.16)**

Multivariate model results for the effects of facet joint ankylosis at baseline on the development of syndesmophytes 2 years later (hypothesis 1) and for the effects of bridging syndesmophytes at baseline on the development of facet joint ankylosis 2 years later (hypothesis 2). Two models were made per hypothesis. Model A looks at the effect of the predictor on the number of newly developed bony lesions (syndesmophyte or facet joint ankylosis) in a vertebral unit regardless of the presence of lesions at baseline. Model B looks at the development of a new lesion (syndesmophyte or facet joint ankylosis) on a vertebral unit adjusting for the presence of lesions at baseline. Vertebral units 4–7 are excluded due to poor visibility of the facet joints. Inflammation is defined as presence of an inflammatory lesion on the vertebral body of a vertebral unit by two out of three MRI readers and as presence of an inflammatory lesion in any of the posterior elements of a vertebral unit (pedicles, processes, facet joints and soft tissues in vertebral units 7–23; only pedicles and soft tissues in vertebral units 1–6) by two out of three MRI readers. Bold values indicate statistical significance. FJA: facet joint ankylosis; OR: odds ratio.

TABLE 2 Multivariable model associations for adjacent-VU analyses of FJA and syndesmophyte development 2 years later and bridging syndesmophytes and FJA development 2 years later

Models	OR (95% CI)	
	1 VU-level shifted ($n = 51$)	2 VU-levels shifted ($n = 51$)
Effect of FJA on increase syndesmophytes on the *VU above* (hypothesis 1A)		
Baseline FJA	**1.96 (1.23, 3.14)**	1.29 (0.79, 2.10)
Baseline vertebral body inflammation	**1.82 (1.24, 2.67)**	**1.93 (1.30, 2.86)**
Effect of FJA on increase syndesmophytes on the *VU below* (hypothesis 1A)		
Baseline FJA	1.55 (0.99, 2.43)	**1.85 (1.25, 2.74)**
Baseline vertebral body inflammation	**1.80 (1.19, 2.71)**	**1.78 (1.20, 2.63)**
Effect of FJA on presence syndesmophytes on the *VU above* (hypothesis 1B)		
Baseline FJA	**2.01 (1.06, 3.82)**	1.19 (0.53, 2.71)
Baseline vertebral body inflammation	**2.39 (1.45, 3.95)**	**2.40 (1.42, 4.05)**
Effect of FJA on presence syndesmophytes on the *VU below* (hypothesis 1B)		
Baseline FJA	**1.89 (1.03, 3.45)**	**2.19 (1.12, 4.31)**
Baseline vertebral body inflammation	**2.61 (1.53, 4.44)**	**2.16 (1.26, 3.68)**
Effect bridging syndesmophyte on increase FJA on the *VU above* (hypothesis 2A)		
Baseline bridging syndesmophyte	**2.56 (1.23, 5.31)**	1.70 (0.84, 3.45)
Baseline posterior elements inflammation	1.97 (0.64, 6.06)	2.05 (0.73, 5.75)
Effect bridging syndesmophyte on increase FJA on the *VU below* (hypothesis 2A)		
Baseline bridging syndesmophyte	**3.11 (1.88, 5.12)**	**2.98 (1.97, 4.50)**
Baseline posterior elements inflammation	2.21 (0.75, 6.54)	1.98 (0.68, 5.79)
Effect bridging syndesmophyte on presence FJA on the *VU above* (hypothesis 2B)		
Baseline bridging syndesmophyte	1.81 (1.01, 3.25)	1.47 (0.93, 2.32)
Baseline posterior elements inflammation	**2.30 (1.12, 4.71)**	**2.29 (1.19, 4.40)**
Effect bridging syndesmophyte on presence FJA on the *VU below* (hypothesis 2B)		
Baseline bridging syndesmophyte	**3.04 (1.94, 4.77)**	**3.13 (1.90, 5.16)**
Baseline posterior elements inflammation	**2.45 (1.20, 5.00)**	**2.51 (1.22, 5.16)**

Multivariable model results for the effects of facet joint ankylosis at baseline on the development of syndesmophytes 2 years later on an adjacent vertebral unit (hypothesis 1) and for the effects of bridging syndesmophytes at baseline on the development of facet joint ankylosis 2 years later on an adjacent vertebral unit (hypothesis 2). Two types of models were made per hypothesis. Model A looks at the effect of the predictor on the number of newly developed bony lesions (syndesmophyte or facet joint ankylosis) in an adjacent vertebral unit regardless of the presence of lesions at baseline. Model B looks at the development of a new lesion (syndesmophyte or facet joint ankylosis) in an adjacent vertebral unit adjusting for the presence of lesions at baseline. The shifting of vertebral units is introduced only between the predictor and the outcome variable, i.e. inflammation at baseline is still added as a predictor for syndesmophytes at follow-up on the same vertebral unit. Facet joint ankylosis scores for vertebral units 4–7 are excluded due to poor visibility of the facet joints. Inflammation is defined as presence of an inflammatory lesion on the vertebral body of a vertebral unit by two out of three MRI readers and as presence of an inflammatory lesion in any of the posterior elements of a vertebral unit (pedicles, processes, facet joints and soft tissues in vertebral units 7–23; only pedicles and soft tissues in vertebral units 1–6) by two out of three MRI readers. Bold values indicate statistical significance. BL: baseline; FJA: facet joint ankylosis; OR: odds ratio; VU: vertebral unit.

for the increase of FJA and 5.54 (3.14, 9.80) for the presence of FJA.

Discussion

In the current study we assessed whether FJA was associated with syndesmophyte development 2 years later (hypothesis 1), and whether fusion of the vertebral bodies in the form of bridging syndesmophytes was associated with FJA (hypothesis 2), with both associations being adjusted for presence of inflammation. We present evidence supporting both hypotheses, with the strongest associations for bridging syndesmophytes being a predictor for FJA. We also found evidence for presence of a dose–response effect in both directions with high ORs when there was extensive presence of bridging syndesmophyte, further supporting the hypotheses. In addition to studying the hypotheses on the same VU, we explored the hypotheses with the outcome on one or two VUs above or below the predictor. We found statistically significant positive associations for five out of eight models for both hypotheses, indicating that FJA or bridging syndesmophytes in an adjacent VU increase risk of syndesmophyte development or FJA. Just as for the main models, ORs are slightly higher for bridging syndesmophytes being a predictor for FJA (hypothesis 2) than for the FJA being a predictor for syndesmophyte development (hypothesis 1).

Table 3 multivariable models associations of dose-response effects between FJA and syndesmophytes

Models	OR (95% CI) ($n = 51$)
Effect of FJA on increase syndesmophytes (hypothesis 1A)	
Baseline FJA—no ankylosis	Ref.
Baseline FJA—1 ankylosed facet joint	1.32 (0.54, 3.22)
Baseline FJA—2 ankylosed facet joints	**2.15 (1.24, 3.27)**
Baseline vertebral body inflammation	**1.87 (1.27, 2.75)**
Effect of FJA on presence syndesmophytes (hypothesis 1B)	
Baseline FJA—no ankylosis	Ref.
Baseline FJA—1 ankylosed facet joint	1.17 (0.25, 5.35)
Baseline FJA—2 ankylosed facet joints	1.86 (0.94, 3.71)
Baseline vertebral body inflammation	**2.30 (1.40, 3.79)**
Effect of bridging syndesmophytes on increase FJA (hypothesis 2A)	
Baseline bridging syndesmophyte—0 affected quadrants	Ref.
Baseline bridging syndesmophyte—1 affected quadrant	2.22 (0.90, 5.46)
Baseline bridging syndesmophyte—2 affected quadrants	**3.09 (1.30, 7.36)**
Baseline bridging syndesmophyte—3 affected quadrants	**4.83 (2.03, 11.52)**
Baseline bridging syndesmophyte—4 affected quadrants	**6.43 (2.95, 14.03)**
Baseline posterior elements inflammation	2.14 (0.69, 6.61)
Effect of bridging syndesmophytes on presence FJA (hypothesis 2B)	
Baseline bridging syndesmophyte—0 affected quadrants	Ref.
Baseline bridging syndesmophyte—1 affected quadrant	**2.35 (1.27, 4.34)**
Baseline bridging syndesmophyte—2 affected quadrants	**3.29 (1.60, 6.77)**
Baseline bridging syndesmophyte—3 affected quadrants	**3.23 (1.23, 8.45)**
Baseline bridging syndesmophyte—4 affected quadrants	**5.54 (3.14, 9.80)**
Baseline posterior elements inflammation	**2.51 (1.22, 5.15)**

Multivariate model results for the effects of facet joint ankylosis at baseline on the development of syndesmophytes 2 years later (hypothesis 1) and for the effects of bridging syndesmophytes at baseline on the development of facet joint ankylosis 2 years later (hypothesis 2). Predictors are categorized by the extent of the bony lesion present: FJA in 0–2 joints and bridging syndesmophytes in 0–4 quadrants. In all models, the category with no presence of the predictor (i.e. zero ankylosed facet joints or no affected quadrants) is the reference for the other categories. Two models were made per hypothesis. Model A looks at the effect of the predictor on the number of newly developed bony lesions (syndesmophyte or facet joint ankylosis) in a vertebral unit regardless of the presence of lesions at baseline. Model B looks at the development of a new lesion (syndesmophyte or facet joint ankylosis) on a vertebral unit adjusting for the presence of lesions at baseline. Vertebral units 4–7 are excluded due to poor visibility of the facet joints. Inflammation is defined as presence of an inflammatory lesion on the vertebral body of a vertebral unit by two out of three MRI readers and as presence of an inflammatory lesion in any of the posterior elements of a vertebral unit (pedicles, processes, facet joints and soft tissues in vertebral units 7–23; only pedicles and soft tissues in vertebral units 1–6) by two out of three MRI readers. Bold values indicate statistical significance. FJA: facet joint ankylosis; OR: odds ratio.

The literature provided little, and somewhat contradictory, information on associations between FJA and syndesmophytes. As we found both syndesmophytes and FJA to be risk factors for subsequent bone formation, our results do not support the notion that FJA is a primary lesion in r-axSpA [7]. On the contrary, syndesmophytes appeared to be stronger risk factors for FJA than vice versa. This is also substantiated by the fact that bridging syndesmophytes are more common than FJA in our study population. With these findings, our study is more in line with the study by Tan *et al.* [8] reporting that syndesmophytes are likely to appear before FJA on a vertebral level. It is important to note, however, that our study population was selected for the presence of at least one syndesmophyte and one inflammatory spinal lesion at baseline, and therefore the results need to be interpreted in this context. Our sample size of individual patients was also modest ($n = 51$), although the use of ldCT allowed assessment of the whole spine of each patient thus yielding a sample size of 1173 VUs. Our imaging assessments were performed twice and with a 2-year interval. It is possible that a longer time interval is needed to fully capture the effects under study. Therefore, future studies are needed to confirm our reported associations and further explore and explain the pathways through which they operate. However, the aforementioned studies used more descriptive statistical methods, assessed smaller parts of the spine and did not include assessments of inflammation. Our study applied statistical methods that disentangle the temporal sequence, control for inflammation, handle the correlations between levels of data, and allow us to evaluate the link between two types of bony lesions at the VU level. We also explored the hypotheses in both directions and in multiple scenarios, looking not only to associations on the same VU but also across VU levels. With this, our study has brought strong arguments to a longstanding debate.

As mentioned above, all our models were adjusted for presence of inflammation. The effect of vertebral body inflammation on the development of syndesmophytes was already known from literature [16–18], and was therefore added to our models. Although inflammation in the posterior elements is well known in r-axSpA [21, 22], its association with FJA was not previously reported. Because of the known link between vertebral body inflammation and syndesmophytes, we suspected inflammation in the posterior elements to have a similar effect on FJA and added it to the models that used FJA as the outcome. In our study population, inflammation in the posterior elements was most frequently present in the thoracic spine, with almost no presence in the cervical and lower lumbar spine and little presence in the upper lumbar spine (Supplementary Fig. S1, available at *Rheumatology* online). Although the association between inflammation in the posterior elements and FJA was not the primary aim of the study, statistically significant positive associations were found in almost half of the models adjusted for it (Tables 1 and 2). These results show that, in our multivariable models, developing FJA is two times as likely when there is inflammation in the posterior elements 2 years prior.

In conclusion, this is the first study to provide evidence pointing to a positive association between FJA and syndesmophyte development and bridging syndesmophytes and FJA development, which exists next to the associations between inflammation and bony lesions. Additionally, this is the first study to report a positive association between inflammation in the posterior elements and FJA. With these results we can imagine a pathway to pathological bone formation in r-axSpA in which inflammation leads to bone formation, after which bone formation leads to additional bone formation. Previous studies have reported several risk factors for syndesmophyte development but have not taken into account other bone formation in the spine. We show that FJA is connected to syndesmophyte development and should therefore also be considered and measured when studying structural damage in the spine.

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Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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