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No relationship between bone mineral density and syndesmophyte formation at the same level in the lumbar spine of patients with radiographic axial Spondyloarthritis

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ABSTRACT

Objective To investigate if in radiographic axial Spondyloarthritis (r-axSpA) low vertebral bone mineral density (BMD) is associated with development of new syndesmophytes at the same vertebral level.

Methods In a post-hoc analysis from the ASSERT trial (infliximab vs placebo), dual-energy X-ray absorptiometry was used to measure baseline BMD (g/cm^2) of the lumbar spine L1 to L4. Syndesmophyte formation was assessed in the same vertebrae on conventional radiographs defined as an increase in modified Stoke Ankylosing Spondylitis Spine Score from 0 or 1 to 2 or 3 after 2 years. Radiographs were scored by two readers. Generalised estimating equations (GEE) adjusted for within-patient correlation across multiple vertebrae, taking potential confounders into account.

Results We analysed 599 vertebrae in 165 r-axSpA patients (78% male, mean (SD) age 38 (10) years, 67% with at least one syndesmophyte anywhere in the spine). In total, 24 to 74 new syndesmophytes developed in 9 (5%) to 30 (18%) patients and 13 (2%) to 39 (7%) vertebrae, if either a syndesmophyte was seen by both or only one of the readers (ie, specific and sensitive definitions) respectively. In multivariable analyses, no association was found between baseline local vertebral BMD and new syndesmophyte formation after 2 years: adjOR (95% CI): 0.56 (0.01, 44.45) (specific definition) and 0.26 (0.03, 2.63) (sensitive definition).

Conclusion In patients with active and established r-axSpA, with an observed low incidence of lumbar spine syndesmophyte formation over 2 years, no relationship was found between baseline BMD and new radiographic syndesmophyte formation at the same vertebra.

Key messages

What is already known about this subject?

- In radiographic axial spondyloarthritis (r-axSpA) it has been hypothesised that inflammation-driven bone loss triggers bone repair but at anatomically distinct sites of the same vertebra (ie, bone loss occurring in the trabecular bone and bone repair in the periosteum).
- Previous studies have reported a general association between systemic low bone mineral density (BMD) and syndesmophyte formation in r-axSpA.

What does this study add?

- By studying, for the first time, the relationship between low BMD and subsequent syndesmophyte formation at the same vertebra, our study is the first step to analyse low BMD as a possible local precursor in the pathogenesis of syndesmophyte development.
- Lower BMD in the lumbar spine was observed in vertebrae that had syndesmophyte formation two years later, however, the association was not statistically significant.

How might this impact on clinical practice or future developments?

- With conventional radiographs and dual-energy X-ray absorptiometry limiting research into the role of BMD on syndesmophyte formation to the lumbar spine, there is a need for sensitive imaging techniques that allow the assessment of both BMD and syndesmophytes in the entire spine.

INTRODUCTION

Radiographic axial Spondyloarthritis (r-axSpA), classically known as Ankylosing Spondylitis (AS), is a chronic inflammatory disease characterised by inflammation in the spine and sacroiliac joints which can lead to irreversible structural damage. Structural damage in r-axSpA is characterised by excessive bone formation. So-called syndesmophytes are the major hallmark lesions, and are associated with the impairment of spinal mobility and functional disability.[1 2]

Paradoxically, bone involvement in r-axSpA comprises not only new bone formation but also the coexistence of bone loss, both contributing to the morbidity of the disease.[3] Bone

loss may occur as local bone erosions in the sacroiliac joints and vertebrae and, as systemic bone loss (osteoporosis), leading to an increased fracture risk and of vertebral fracture in particular.[3] Osteoporosis is a common complication of r-axSpA,[4] that can occur not only as consequence of decreased physical activity and functional capacity related to pain, stiffness, and ankylosis, but is also present early in the disease,[5 6] directly or indirectly related to inflammation.[6 7]

What leads to simultaneous bone loss and bone formation is still poorly understood. According to a recently proposed model, inflammation acts as an inhibitory mechanism on the normal bone cycle making osteoblasts in the trabecular bone incapable of compensating for the bone loss.[8] As a consequence, periosteal osteoprogenitor cells are called upon to stabilise the spine by forming syndesmophytes eventually bridging the intervertebral space. Thus, the anabolic reaction that characterises structural disease progression in r-axSpA might be a reactive effort to increase spinal stability, with the impairment in mobility as the 'price to pay' in this equation. In summary, according to this model, inflammation-driven bone loss triggers bone repair but at anatomically distinct sites of the same vertebra (ie, bone loss occurring in the trabecular bone and bone repair in the periosteum).

Previous studies have reported a general association between systemic low bone mass and spinal structural damage in r-axSpA.[9 10] Moreover, low bone mineral density (BMD) of the hip and spine has been independently associated with the development of new cervical or lumbar syndesmophytes in young axSpA patients (below 50 years of age).[11] However, none of the previous studies assessed the possible association between bone loss and new bone formation at the same individual vertebra which is central in the above-exposed theoretical model.[8]

Low BMD can be seen as solely a comorbidity/complication of axSpA patients or as a crucial part in the pathogenesis of the structural damage. The latter could mean that if we treat inflammation early and, ideally before any bone loss, we can likely prevent structural damage in axSpA.

Thus, the purpose of this study was to investigate the relationship between BMD and the development of syndesmophytes at the same vertebra, 2 years later, in patients with r-axSpA. By using a multilevel analysis, we aim to test the hypothesis that inflammation-driven vertebral bone loss may pathologically enhance local ectopic bone formation.

METHODS

Study population

For this study, we analysed an 80% random sample of the AS Study for the Evaluation of Recombinant Infliximab Therapy (ASSERT) that we used in our previous analysis.[12–14] Briefly, ASSERT was a 24-week multicentre, randomised, double-blind, placebo-controlled trial with infliximab that included subjects with r-axSpA (according to the modified New York criteria), with Bath AS Disease Activity Index[15] (BASDAI) ≥4 (range 0–10) and a spinal pain score ≥4 (range 0–10), with an open extension until 2 years with all patients treated with infliximab. The included patients in the present study should have performed a baseline dual-energy X-ray absorptiometry (DXA) at the lumbar level, as well as spinal conventional radiographs (CRs) at baseline and 2 years.

Imaging assessments

BMD assessment

DXA was used to assess baseline BMD of the lumbar spine using an anteroposterior projection at L1-L4. All measurements were taken by experienced operators using standardised procedures for patient positioning. For this study, we considered the number of grams of bone mineral per square centimetre (g/cm^2) for each individual vertebra from L1 to L4.

Radiographic assessment

Syndesmophyte formation from baseline to 2 years was evaluated on CRs of the spine, using the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS).[16 17] CRs were scored by two trained readers, who were blinded to clinical information and chronological order. Inter-reader reliability was previously computed, and the intra-class correlation coefficients were 0.96 (baseline), 0.97 (102 weeks) and 0.86 (102 weeks change).[13] According to the mSASSS, the anterior vertebral corners (VCs) of the cervical (lower border of C2 to upper border of T1) and lumbar (lower border of T12 to upper border of S1) segments (a total of 24 VCs) were scored at a lateral view, for the presence of erosion and/or sclerosis and/or squaring (1 point), syndesmophyte (2 points) and bridging syndesmophyte (3 points). The total score can range from 0 to 72. For this study, only lumbar scores of four vertebrae were considered to match the same vertebrae assessed by DXA (a total of 8 VCs). New syndesmophyte formation was defined per VC as a change from a baseline mSASSS score of 0 or 1 to either 2 or 3 at 2 years, that is, the formation of a syndesmophyte or a bridge at a VC that was previously without a syndesmophyte. As the measurements of BMD correspond to a vertebra (L1 to L4), the individual scores for each of the VCs were transformed into the vertebral level (considering the upper and lower border of the same vertebra). Thus, for the analyses, we categorised syndesmophyte formation, as 0, if no syndesmophyte formation was reported in any of the two VCs of the same vertebra and, as 1, if syndesmophyte formation was reported in at least 1 of the two VCs of the same vertebra.

MRI (MRI) assessment

MRIs were previously scored by two readers at baseline.[14] T1-weighted and short tau inversion recovery (STIR) sequences were assessed and the VCs of L1 to L4 were scored for the presence/absence of vertebral corner

inflammation (VCI) and vertebral corner fat deposition (VCFD), according to the methodology applied in our recently published study.[14] Presence of VCI and VCFD separately scored by both readers was used. Individual scores for each of the VCs were transformed into the vertebral level, defined as 0, if none of the VCs of the same vertebra were scored with VCI or VCFD and, as 1, if at least one of the two VCs of the vertebra was scored with VCI or VCFD, respectively.

Outcome definition

Four definitions for the outcome 'syndesmophyte formation' according to the reader are possible: (1) new syndesmophyte formation according to absolute agreement of both readers (specific definition); (2) new syndesmophyte formation reported by at least one of the readers (sensitive definition); (3) new syndesmophyte formation according to reader 1 and, (4) new syndesmophyte formation according to reader 2. The main analysis was performed using a definition aiming at specificity. The other definitions were used in secondary analyses.

Statistical analysis

Data were analysed at the patient level and at the vertebral level in the four vertebrae (L1 to L4) that were assessed by DXA and CRs. Vertebrae exhibiting abnormalities, such as fracture or surgical alteration, and vertebrae with syndesmophytes at baseline were excluded from the analysis. Frequencies of patients with new syndesmophytes, as well as of the number of new syndesmophytes per vertebra were computed. Univariable and multivariable analyses were performed using a multilevel analysis approach to investigate the relationship between baseline BMD at a vertebral level and the syndesmophyte formation according to the above-specified definitions. Generalised estimating equations (GEEs) were applied making use of all data, across all levels, that is, patient level and vertebral level.[18] Multilevel analysis adjusts for within-patient correlation across different vertebral levels, that is, adjusting for the dependence of observations arising from multiple measurements in different vertebrae of the same patient. The following confounders were considered: age, gender, disease duration, Human Leucocyte Antigen (HLA-B27), baseline disease activity (Ankylosing Spondylitis Disease Activity Score (ASDAS)—computed using the formula), trial medication during the first 24 weeks (infliximab vs placebo), treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) varying over time (yes/no), presence of inflammation in MRI at baseline, presence of fat deposition in MRI at baseline and presence of syndesmophytes at baseline anywhere in the spine (defined as a patient with at least one VC with an mSASSS score of ≥2). Absolute agreement of the readers was used for both radiographic and MRI case definitions. These confounders were chosen upfront based on knowledge from other studies, and not necessarily based on the univariable analysis.[19 20] Statistical analyses were performed using Stata. Data were accessed via the 'YODA Project' online platform (https://yoda.yale.edu).

RESULTS

We included a total of 165 r-axSpA patients who had a baseline DXA of the lumbar spine as well as spinal CRs at baseline and two years later available. Table 1 summarises the baseline characteristics. At baseline these patients had a mean (SD) age of 38.1 (9.6) years, 78% were male, 90% were HLA-B27 positive, 67% of them had at least one syndesmophyte anywhere in the spine, overall patients had high or very high disease activity (mean (SD) ASDAS of 4.0 (0.9)). MRI vertebral corner inflammation was reported in at least one lumbar vertebral corner in one-fourth of the patients. The mean BMD of the lumbar spine of all included patients was 1.0 (0.2) g/cm^2.

Incidence of new syndesmophyte formation after two years of follow-up

Out of a total of 660 possible vertebrae (4 lumbar vertebrae from 165 patients), 599 vertebrae were included in the main analysis, after excluding vertebrae exhibiting abnormalities at baseline (fracture (n=1); syndesmophytes (n=60), of which 56 were bridging syndesmophytes).

Table 1 Baseline characteristics of r-axSpA patients with baseline dual-energy X-ray absorptiometry and baseline and 2-year spinal radiographs

Assessment	N=165†
Male, no. (%)	128 (77.6)
Age, years	38.1 (9.6)
Disease duration, years	10.0 (7.9)
BMI, Kg/m^2	25.5 (4.1)
HLA-B27 positive, no. (%)	148 (90.2)
CRP, mg/L	24.3 (29.4)
BASDAI (0–10)	6.4 (1.5)
ASDAS	4.0 (0.9)
mSASSS	13.9 (12.7)
Patients treated with NSAIDs, no. (%)	144 (87.3)
Patients treated with bisphosphonates, no. (%)	5 (3.0)
Patients treated with calcium and/or vitamin D, no. (%)	8 (4.8)
Patients with baseline syndesmophytes, no. (%)‡	111 (67.3)
Patients with lumbar MRI VCI, no. (%)§	42 (25.8)
Patients with lumbar MRI VCFD, no. (%)§	55 (33.7)
Mean lumbar spine BMD (g/cm^2)	1.0 (0.2)

†Data are presented as mean (SD) or n (%).
‡Syndesmophytes anywhere in the spine defined as a patient with at least one vertebral corner that received an mSASSS of ≥2, according to the absolute agreement of readers.
§Defined as a patient with at least one lumbar vertebral corner with MRI VCI or VCFD (absolute agreement of the readers), respectively.
ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BMD, Bone mineral density; BMI, Body mass index; HLA, Human leucocyte antigen; mSASSS, Modified Stoke Ankylosing Spondylitis Spine Score; NSAIDs, Nonsteroidal anti-inflammatory drugs; VCFD, Vertebral corner fat deposition; VCI, Vertebral corner inflammation.

According to the specific definition a total of 24 new syndesmophytes developed at the 2-year follow-up (L1, n=6; L2, n=6; L3, n=7 and L4, n=5), in 9 (5%) patients and 13 (2%) vertebrae. Considering the definition aiming at sensitivity, a total of 74 syndesmophytes had developed after 2 years as reported by at least one of the readers (L1, n=21; L2, n=18; L3, n=17 and L4, n=18), corresponding to 30 (18%) patients and 39 (7%) vertebrae.

Relationship between baseline BMD (g/cm^2) and new syndesmophyte formation after two years

Lower BMD was observed in vertebrae that had syndesmophyte formation, but no significant association was found between baseline BMD (g/cm^2) and new syndesmophyte formation after 2 years.

In multivariable analysis the absence of a significant association was consistent across all the outcome definitions as reflected in a wide CI: syndesmophyte formation according to both readers (specific definition): adjOR 0.56 (0.01, 44.45), new syndesmophyte formation reported by at least one of the readers (sensitive definition): adjOR 0.26 (0.03, 2.63), new syndesmophyte formation according to reader one adjOR 0.07 (0.00, 1.56) and, new syndesmophyte formation according to reader two 0.63 (0.13, 13.68) (tables 2 and 3).

The association between other independent variables and new syndesmophyte formation varied across the four different outcome definitions (tables 2 and 3). Syndesmophyte formation according to its sensitive definition was found to be significantly associated with age (adjOR: 1.04, 95% CI: 1.00 to 1.09), the presence of baseline MRI VCI at the vertebral level (adjOR: 4.32, 95% CI: 1.95 to 9.60) and the baseline presence of syndesmophytes anywhere in the spine at the patient level (adjOR: 3.14, 95% CI: 1.14 to 8.66), confirming known relationships. Also, syndesmophyte formation according to reader one was significantly associated with the presence of baseline MRI VCI at the vertebral level (adjOR: 5.84, 95% CI: 2.21 to 15.47) and the baseline presence of syndesmophytes anywhere in the spine at the patient level (adjOR: 5.97, 95% CI: 1.67 to 21.30).

DISCUSSION

In this multilevel analysis of patients with active and severe r-axSpA, we aimed to investigate the possible relationship between bone loss and subsequent syndesmophyte formation at the same vertebra after 2 years. Consistent with the theoretical model of inflammation-driven bone loss and subsequent syndesmophyte formation at the same level, lower BMD was observed in vertebrae that had syndesmophyte formation, however, the association was not statistically significant regardless of the reader definition.

To conclude if these results refute the theory on the relationship between inflammation-driven bone loss and subsequent syndesmophyte formation at the same vertebra as an attempt of stabilising the spinal structure,[8] a detailed discussion of the results is necessary.

Firstly, in our study, a relatively low incidence of new syndesmophyte formation was found. CRs are considered the current standard for the assessment of syndesmophytes in r-axSpA[21] and the mSASSS[16] is currently the best available scoring method.[17] For a sufficient sensitivity to change in depiction of structural spinal changes in r-axSpA when using CRs, a minimal observation period of 2 years is required.[22] Both requirements are fulfilled in our study which included a substantial number of r-axSpA

Table 2 Relationship between baseline BMD and 2-year syndesmophyte formation based on agreement between both readers

	New radiographic syndesmophyte formation according to both reader 1 and reader 2	
Independent variables	**Univariable analysis—adjOR (95% CI)**	**Multivariable analysis—adjOR (95%)**
BMD (g/cm^2)	0.12 (0.00, 9.94)	0.56 (0.01, 44.45)
Age (years)	1.05 (0.99, 1.12)	1.03 (0.95, 1.11)
Gender (male)	1.60 (0.31, 8.30)	0.82 (0.10, 6.85)
Disease duration (years)	1.06 (1.01, 1.11)*	1.05 (0.97, 1.14)
ASDAS	1.62 (0.72, 3.65)	1.79 (0.66, 4.86)
HLA-B27	0.27 (0.05, 1.38)	0.13 (0.02, 0.89)
Treatment with NSAIDs	0.79 (0.16, 3.85)	0.41 (0.07, 2.47)
Treatment with infliximab	1.81 (0.22, 14.98)	1.82 (0.22, 15.31)
Presence of MRI VCI at baseline†	3.63 (0.87, 15.31)	4.00 (0.99, 16.13)
Presence of MRI VCFD at baseline†	0.55 (0.13, 2.29)	0.69 (0.16, 3.01)
Presence of syndesmophytes at baseline†,‡	8.51 (1.06, 68.13)*	20.20 (0.96, 424.63)

adjOR, Adjusted OR; ASDAS, Ankylosing Spondylitis Disease Activity Score; BMD, Bone mineral density; CI, Confidence Interval; GEE, Generalised estimated equations; NSAIDs, Nonsteroidal anti-inflammatory drugs; VCFD, Vertebral corner fat deposition; VCI, Vertebral corner inflammation.

†Radiographic and MRI case definitions aiming at specificity were used (absolute agreement of the readers).

‡Syndesmophytes anywhere in the spine defined as a patient with at least one vertebral corner that received a modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) of ≥2, according to the absolute agreement of readers. *p<0.05.

Table 3 Relationship between baseline BMD and 2-year syndesmophyte formation as reported by at least one of the readers (secondary analysis)

	New radiographic syndesmophyte formation according to reader 1 or reader 2	
Variables	**Univariable analysis—adjOR (95% CI)**	**Multivariable analysis—adjOR (95% CI)**
BMD (g/cm^2)	0.35 (0.04, 2.89)	0.26 (0.03, 2.63)
Age (years)	1.05 (1.01, 1.08)*	1.04 (1.00, 1.09)*
Gender (male)	1.99 (0.79, 5.06)	1.42 (0.50, 4.01)
Disease duration (years)	1.03 (0.99, 1.07)	1.00 (0.96, 1.05)
ASDAS	1.29 (0.84, 1.98)	1.09 (0.63, 1.87)
HLA-B27	0.58 (0.17, 1.93)	0.54 (0.15, 1.89)
Treatment with NSAIDs	1.16 (0.38, 3.53)	0.82 (0.21, 3.13)
Treatment with infliximab	1.01 (0.40, 2.56)	1.11 (0.45, 2.69)
Presence of MRI VCI at baseline†	3.80 (1.92, 7.55)*	4.32 (1.95, 9.60)*
Presence of MRI VCFD at baseline†	1.50 (0.74, 3.01)	1.23 (0.60, 2.54)
Presence of syndesmophytes at baseline†,‡	4.10 (1.48, 11.35)*	3.14 (1.14, 8.66)*
	New radiographic syndesmophyte formation according to reader 1	
Variables	**Univariable analysis—adjOR (95% CI)**	**Multivariable analysis—adjOR (95% CI)**
BMD (g/cm^2)	0.10 (0.00, 1.34)	0.07 (0.00, 1.56)
Age (years)	1.04 (1.00, 1.09)*	1.05 (1.00, 1.10)
Gender (male)	1.63 (0.57, 4.71)	1.17 (0.36, 3.86)
Disease duration (years)	1.03 (0.98, 1.08)	1.01 (0.96, 1.06)
ASDAS	1.27 (0.75, 2.13)	1.00 (0.49, 2.02)
HLA-B27	0.45 (0.13, 1.52)	0.39 (0.10, 1.52)
Treatment with NSAIDs	1.60 (0.48, 5.30)	1.27 (0.27, 5.93)
Treatment with infliximab	1.30 (0.39, 4.36)	1.24 (0.40, 3.83)
Presence of MRI VCI at baseline†	4.05 (1.58, 10.38)*	5.84 (2.21, 15.47)*
Presence of MRI VCFD at baseline†	1.24 (0.50, 3.06)	1.10 (0.41, 2.90)
Presence of syndesmophytes at baseline†,‡	6.39 (1.87, 21.84)*	5.97 (1.67, 21.30)*
	New radiographic syndesmophyte formation according to reader 2	
Variables	**Univariable analysis—adjOR (95% CI)**	**Multivariable analysis—adjOR (95% CI)**
BMD (g/cm^2)	0.66 (0.18, 10.29)	0.63 (0.13, 13.68)
Age (years)	1.05 (1.00, 1.10)*	1.04 (0.98, 1.10)
Gender (male)	2.26 (0.64, 7.95)	1.38 (0.28, 6.84)
Disease duration (years)	1.05 (1.00, 1.09)*	1.02 (0.97, 1.08)
ASDAS	1.53 (0.87, 2.67)	1.63 (0.85, 3.12)
HLA-B27	0.35 (0.09, 1.36)	0.26 (0.06, 1.23)
Treatment with NSAIDs	0.71 (0.18, 2.70)	0.42 (0.09, 1.86)
Treatment with infliximab	0.91 (0.29, 2.83)	1.13 (0.38, 3.38)
Presence of MRI VCI at baseline†	1.65 (1.04, 6.76)*	2.62 (0.90, 7.63)
Presence of MRI VCFD at baseline†	1.17 (0.50, 2.76)	1.02 (0.46, 2.27)
Presence of syndesmophytes at baseline†,‡	3.07 (0.83, 11.40)	2.88 (0.66, 12.70)

adjOR, adjusted OR; ASDAS, Ankylosing Spondylitis Disease Activity Score; BMD, Bone mineral density; CI, Confidence Interval; GEE, Generalised estimated equations; NSAIDs, Nonsteroidal anti-inflammatory drugs; VCFD, Vertebral corner fat deposition; VCI, Vertebral corner inflammation.

†Radiographic and MRI case definitions aiming at specificity were used (absolute agreement of the readers).

‡Syndesmophytes anywhere in the spine defined as a patient with at least one vertebral corner that received a modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) of ≥2, according to the absolute agreement of readers. *p<0.05.

patients. However, to assess our research question, syndesmophyte formation on only four lumbar vertebrae could be used for analysis.

Moreover, we have previously shown in the Sensitive Imaging in Ankylosing Spondylitis (SIAS) cohort the limited sensitivity of CRs to assess new or growing

syndesmophytes when compared to CT (CT).[23] Thus, it is plausible that, in part, the low incidence of syndesmophyte formation reported in our study may be related to the low sensitivity of CRs in detecting structural damage progression. This is further emphasised by the fact that, in SIAS, most of the new syndesmophytes were detected by low-dose CT (ldCT) in the thoracic spine[23] (a region neither assessed by the mSASSS, nor by the DXA).

In our study, the mean BMD (L1 to L4) of 1.00 (0.19) is similar to what is reported in other r-axSpA cohorts[4] and only slightly lower to what is expected for a healthy population of equivalent age and gender,[24] probably meaning that no substantial bone loss was captured in the included patients. This is likely reflected in the relatively low number of patients receiving bisphosphonate therapy.

While the most appropriate and valid method to assess BMD in patients with advanced r-axSpA is still unclear, DXA is considered an accurate, repeatable and quantitative method to assess BMD at the spine and hip.[25] Notwithstanding, as DXA measures both vertebral trabecular and cortical BMD it has been shown that new bone formation and aberrant hyperostosis (including osteophytes) artificially increase BMD, in particular when using anteroposterior (instead of lateral) projections of lumbar spine in advanced r-axSpA.[26] In an effort to avoid this pitfall, we sensitively excluded any vertebra with syndesmophytes at baseline. This choice may have also added to the low incidence of new syndesmophytes, as a higher structural damage progression is expected in vertebrae with syndesmophytes at baseline.[27] In fact, and also observed in our study, syndesmophyte formation tends to occur in more than one VC of the same vertebra.[27]

Our results should be interpreted in light of some other limitations. Only lumbar vertebrae (L1 to L4) were possible to assess as those were the ones in which we could match the measurements of vertebral BMD by DXA and radiographic assessments. This may have contributed to the wide CIs observed, possibly pointing out to insufficient study power. On the other hand, we were able to reproduce known predictors of syndesmophyte formation such as inflammation on MRI but only in the sensitive outcome definitions and not in the specific outcome definition which was the primary analysis.

It has been shown in several prospective studies, including the ASSERT trial, and further confirmed in a recent meta-analysis that BMD increases with TNF-inhibitors.[28 29] To minimise the potential increase of BMD over time with infliximab, we only used BMD as measured at baseline (before starting infliximab). However, we cannot exclude that the increased BMD overtime has interfered with the relationship between low BMD and syndesmophyte formation at 2 years. On the other hand, the anti-inflammatory effects of TNF-inhibitors can also possibly halt syndesmophyte formation, and thus trial treatment (infliximab vs placebo) was included as a confounder in our analyses.[30] BMD in patients with r-axSpA is also influenced by the traditional risk factors for osteoporosis, that were not taken into account in this analysis either because data were not available (eg, smoking) or because they are not associated with the outcome syndesmophyte formation and therefore were not considered as confounders by definition.[4]

Overall strengths of our study include: a uniquely large population of patients with r-axSpA with active and established disease and, thus with a theoretical higher likelihood of both bone loss due to inflammation and subsequent syndesmophyte formation; independent and blinded scoring of CRs and MRIs; the use of a comprehensive methodology to test the outcome, including both specific and sensitive definitions; the use of a statistical approach that adjusts for the dependence of observations in the same patient/vertebra and, also the fact that we have adjusted the analyses for multiple well-known potential confounders.

Taken together, we have insufficient evidence to refute the theory on the relationship between inflammation-driven bone loss and subsequent syndesmophyte formation at the same vertebra. This research question should be further studied, ideally using comprehensive imaging methods that allow the assessment of syndesmophytes in the whole spine.

LdCT is a good candidate for this purpose. While new bone formation in the spine of patients with r-axSpA can be assessed reliably using CT Syndesmophyte Score (CTSS) in ldCT,[31] Hounsfield units (HU) or scanographic bone attenuation coefficients (SBAC) can be assessed in CT scans as they correlate with BMD and, normative data have been defined throughout the spine.[32 33] Indeed, combining these two methods could potentially allow assessment of both BMD and syndesmophytes in all segments of the spine.

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prepared the first version of the manuscript. DvdH, SR and FvG supervised and contributed to all steps of the work. All authors critically interpreted the results, reviewed the draft versions and gave their approval of the final version of the manuscript.

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