Positive correlation between inflammation on sacroiliac joint MRI and serum C-terminal telopeptide of type-I collagen in ankylosing spondylitis but not in non-radiographic axial spondyloarthritis

K.Y. Kang[1,2], J.-Y. Jung[3], Y.S. Hong[1,2], J.H. Ju[1], S.-H. Park[1]

[1]Division of Rheumatology, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul; [2]Division of Rheumatology, Department of Internal Medicine, Incheon Saint Mary's Hospital, The Catholic University of Korea, Incheon, Seoul; [3]Department of Radiology, College of Medicine, The Catholic University of Korea, Seoul, South Korea.

Abstract

Objective

To identify the clinical disease activity scores and laboratory markers that best reflect magnetic resonance imaging (MRI)-determined sacroiliac joint (SIJ) inflammation in ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nr-axSpA).

Methods

This cross-sectional study included all consecutive patients who presented with axial spondyloarthritis in 2013–2015. All underwent SIJ MRI. The bone marrow oedema in the inflammatory lesions on MRI was scored using the SPondyloArthritis Research Consortium of Canada (SPARCC) method. Bone-specific alkaline phosphatase (BALP), serum C-terminal telopeptide of type-I collagen (sCTX-I), and inflammatory markers were measured. Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Ankylosing Spondylitis Disease Activity Score (ASDAS) were assessed. The correlations between the MRI-determined SIJ inflammation scores and disease activity scores and laboratory variables were evaluated.

Results

Of the 81 patients with axSpA, 45 had AS and 36 had nr-axSpA. The AS and nr-axSpA groups did not differ in terms of disease activity scores, physical functional index, or MRI-determined SIJ inflammation. Erythrocyte sedimentation rate, C-reactive protein, and ASDAS correlated with MRI inflammatory scores in nr-axSpA but not in AS. sCTX-I correlated with MRI-determined SIJ inflammatory scores in AS only. BASDAI and BALP levels did not associate with MRI inflammatory scores in either group. Multivariate analysis showed that sCTX-I associated independently with MRI inflammatory score in AS (β=17.047, p=0.038).

Conclusion

Inflammatory markers and ASDAS correlated with active sacroiliitis on MRI in nr-axSpA only. In AS, only sCTX-I correlated with active inflammation on SIJ MRI. sCTX-I may be useful as a marker of objective inflammation in AS.

Key words

C-terminal telopeptide of type-I collagen, magnetic resonance imaging, ankylosing spondylitis, axial spondyloarthritis, SPondyloArthritis Research Consortium of Canada

Kwi Young Kang, MD, PhD
Joon-Yong Jung, MD, PhD
Yeon Sik Hong, MD, PhD
Ji Hyeon Ju, MD, PhD
Sung-Hwan Park, MD, PhD

Please address correspondence to:
Dr Sung-Hwan Park,
Division of Rheumatology,
Department of Internal Medicine,
Seoul St. Mary's Hospital,
The Catholic University of Korea,
505, Banpo-Dong, Seocho-Gu,
137-040 Seoul, Republic of Korea.
E-mail: rapark@catholic.ac.kr

Received on July 14, 2016; accepted in revised form on September 29, 2016.

Funding: this work was supported by a grant from the Basic Science Research Program through the National Research Foundation of Korea (NRF), which is funded by the Ministry of Education, Science and Technology (NRF-2014R1A1A1006695).

Competing interests: none declared.

Introduction

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease that is characterised by prominent involvement of the spine or sacroiliac joints (SIJs) or both. AxSpA includes two major forms, as defined by the Assessment of Spondyloarthritis International Society (ASAS) classification criteria (1): non-radiographic (nr) axSpA, which lacks definite sacroiliitis on conventional radiographs, and ankylosing spondylitis (AS), which is characterised by definite sacroiliitis on conventional radiographs (2).

AxSpA is the result of a complex interplay between the inflammatory forces that favour new bone formation and those that favour osteoporosis. As a result, tools that objectively measure the inflammation in axSpA are needed. One possibility is fat-suppressed magnetic resonance imaging (MRI), which was developed recently. This imaging modality directly and non-invasively visualises inflammation-related features, including those in axial joints (3). At present, MRI of the SIJs is the best way to diagnose and classify axSpA, especially in nr-axSpA (4, 5). This is because it is the only imaging tool that can visualise bone marrow oedema (BME), which is a hallmark of sacroiliitis (6). Several clinical trials have also shown that MRI of the SIJs measures the anti-inflammatory efficacy of various therapies in axSpA with high reliability and discrimination (7, 8). There is also some evidence that the inflammatory lesions in the SIJs and spine that can be detected by MRI may help to predict the later development of structural damage (9). It may be useful for selecting those patients who are most likely to respond to tumour necrosis factor (TNF) inhibitors and those who should continuously use non-steroidal anti-inflammatory drugs (NSAIDs).

The MRI-determined inflammatory score was suggested as a more objective measure of disease activity than clinical activity scores. Clinical activity scores are hampered by the fact that inflammatory back pain symptoms can be difficult to distinguish from back pain symptoms that are due to mechanical causes, especially since back pain symptoms due to inflammation and mechanical causes can occur simultaneously in the same patient. Moreover, self-reported measures can be influenced by ankylosis and secondary degenerative changes in AS. These problems mean that if disease activity is monitored using clinical evaluation only, the true nature of a patient's symptoms can be misinterpreted, thus resulting in inappropriate treatment. Therefore, appropriate management decision-making requires concomitant measurement of more objective inflammation variables. Although MRI used as the most sensitive modality for diagnosing and monitoring objective inflammation, it is costly and/or not widely available. Therefore, it would be useful to identify the disease activity scores and/or laboratory biomarkers that objectively reflect inflammation on MRI: such variables could help to identify the patients who are most likely to respond to biological agents and to predict future structural damage.

Several studies have assessed whether the MRI-measured inflammation in the SIJ correlates with clinical disease activity scores and/or several laboratory markers (10-13). Correlations between SIJ MRI inflammatory scores at baseline and disease activity were not detected (11-13). However, the numbers of patients in these studies were too small to conclude whether disease activity scores accurately reflect objective sacroiliitis. In relation to laboratory markers, two studies have shown that C-reactive protein (CRP) correlates moderately well with MRI inflammation (13, 14). Notably, one of these was the recent study by Weiss *et al*., who showed that CRP only correlated with SIJ MRI inflammatory score in axSpA patients with a short symptom duration (≤4 years); this correlation was not observed in patients with a long symptom duration (13). This suggests that correlations between MRI-measured inflammation and biomarker and/or disease activity scores change according to the disease advances. However, to date, studies that compare AS and nr-axSpA in terms of the disease activity scores, inflammatory markers, and bone markers that best reflect the MRI SIJ inflammatory score have not yet been performed.

The aims of this cross-sectional study were to identify the disease activity scores and laboratory markers that best reflect objective SIJ inflammation in patients with AS and nr-axSpA and to compare AS and nr-axSpA patients in terms of the disease activity scores and laboratory markers that best reflect objective SIJ inflammation. For this, the correlations between inflammation on SIJ MRI and clinical disease activity scores and laboratory variables were determined.

Methods

Patient selection

Consecutive patients who presented with axSpA to our tertiary care hospital (Incheon Saint Mary's Hospital) between August 2013 and July 2015 were recruited. All were diagnosed with axSpA according to the ASAS axSpA criteria (1). Patients were excluded if they were pregnant, had thyroid or parathyroid disorders, had chronic renal or liver disease, or were being treated with bisphosphonate, calcium, or vitamin D. All patients were checked to determine whether they fulfilled the modified New York criteria for the classification of AS (2). All patients underwent MRI scans of both SIJs at enrollment. The study was approved by the ethics committee of Incheon Saint Mary's Hospital, Catholic University of Korea (XC13RIMI0129O) and was conducted in accordance with the ethical principles of the 1975 Declaration of Helsinki. The requirement for informed consent was waived because the usual clinical management of the patients was not altered.

Clinical assessments

The following demographic data were collected: age, sex, time after symptom onset, years from the diagnosis of axSpA, the presence of HLA-B27, smoking status, family history, and current medications. The following disease activity scores were measured: patient global assessment (PGA) and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (15). Both scores were recorded on a visual analogue scale ranging from 0 to 10. The Ankylosing Spondylitis Disease Activity Score (ASDAS), which includes the erythrocyte sedimentation rate (ESR) and CRP level, was also calculated using the formula that was described previously (16). Functional activity was assessed using the Bath Ankylosing Spondylitis Functional Index (BASFI) (17).

Laboratory assessments

Laboratory assessments were performed at the time of the MRI assessment. Blood samples were obtained in the morning after 8 hours of fasting. The ESR (mm/hr) and serum CRP (mg/l) levels were measured. Bone turnover was studied by measuring the levels of the bone resorption marker serum cross-linked C-terminal telopeptide of type-I collagen (sCTX-I) and the bone formation marker serum bone-specific alkaline phosphatase (BALP). sCTX-I was measured using an electrochemiluminescence immunoassay (ECLIA; Elecsys 2010 Roche Diagnostics, Mannheim, Germany) according to the manufacturer's protocol. Serum BALP was measured using an enzyme immunoassay (MicroVue BAP; Quidel, San Diego, CA, USA) according to the manufacturer's protocol.

Radiological assessments

For all patients, radiographs of the cervical spine, lumbar spine, and pelvis were obtained at the time of the MRI assessment. Lateral views of the cervical and lumbar spine were scored according to the modified Stoke AS Spinal Score (mSASSS). To obtain the mSASSS, the anterior vertebral corners of the cervical (C2 lower-T1 upper) and lumbar (T12 lower-S1 upper) spine were scored (0–3 points each) (18). The mSASSS was calculated as the sum of the scores at all individual sites (range 0–72). Sacroiliitis was scored from right- and left-sided pelvic radiographs using the modified New York criteria (2). The average score for both sides was used for analysis. Sacroiliitis and mSASSS were scored by a single trained expert who was blinded to the patient characteristics (KY Kang).

MRI protocol

MRI of the SIJ was performed at enrollment Images were obtained using a 3.0 T MRI unit (Verio/Skyra; Siemens Medical, Erlangen, Germany) and a body flexed array coil (Siemens Medical, Erlangen, Germany). Assessment of the lesions in the SIJ was based on T1-weighted turbo spin echo (TSE) MRI sequences and T2-weighted FS TSE sequences. The sequence protocol was as follows: semi-coronal (along the long axis of the sacral bone) TSE [slice thickness (ST) 3 mm; repetition time/echo time (TR/TE) 636/11 ms] and semi-coronal T2-weighted FS TSE (ST 3 mm; TR/TE 5210/55 ms).

Semi-quantitative assessment of MRI findings

The inflammation on the semi-coronal T2-weighted FS TSE sequences on SIJ MRI was quantified using the SPondyloArthritis Research Consortium of Canada (SPARCC) scoring method (19). All scores were measured by an experienced musculoskeletal radiologist (JY Jung) who was blinded to the patient characteristics. The SIJs were scored using the SPARCC method on six consecutive coronal slices that depicted the synovial portion of the joint. The presence of BME is scored from 0 to 48, the presence of deep BME (defined as ≥1 cm) is scored from 0 to 12, and the presence of intense BME (defined as being comparable to, or greater than, the appearance of blood in presacral veins) is scored from 0 to 12. Total inflammatory score is defined as a sum of BME score, deep BME score and intense BME score. The maximum score is 72.

Statistical analysis

Continuous data were expressed as mean±SD, and categorical data were expressed as percentages. Patient groups were compared in terms of continuous and categorical variables using the Mann-Whitney U-test and Chi-squared test, respectively. Spearman's correlation coefficient was used to analyse correlations between variables. Multivariate linear regression analysis was performed to ascertain the association between inflammation on SIJ MRI and disease activity score and laboratory variables after adjusting for potential confounders. All variables with a p-value of <0.05 in univariate analysis

were incorporated as explanatory variables. Variables with a p-value of <0.05 were entered into the multivariate linear regression analyses (enter method). A p-value of <0.05 was considered to indicate statistical significance. All statistical analyses were performed using PASW statistics 18 (SPSS Inc., Chicago, IL, USA).

Results

Total eighty-one patients with axSpA were enrolled. Table I shows their characteristics. All were over 20 years of age (the mean age was 32 years), 66 (82%) were male, and the mean symptom duration and time after diagnosis of axSpA were 5.6±7.9 and 1.5±3.0 years, respectively.

AS and nr-axSpA were diagnosed in 45 and 36 patients, respectively. The two groups did not differ in terms of demographic characteristics (Table I). However, compared with the patients with nr-axSpA, the patients with AS had higher ESRs (p=0.012) and tended to have higher CRP levels, although the latter did not achieve statistical significance (p=0.087). The patients with AS also had a higher sacroiliitis grade, a greater mSASSS, and more syndesmophytes (all p<0.001). The two groups did not differ in terms of disease activity scores, physical function index, or frequency of current treatment with NSAIDs or sulfasalazine. None of the patients received TNF inhibitors.

Table II shows the SPARCC scores for acute inflammatory lesions on SIJ MRI. Most patients (73%) had SI inflammation, as measured by MRI. However, the nr-axSpA and AS groups did not differ in terms of frequency of active SI inflammation (26/36, 74% *vs*. 33/45, 72%; p=0.803). The mean BME, deep BME, intense BME, and total inflammatory scores of the whole cohort were 7.2±8.1, 1.5±2.1, 0.8±1.8, and 9.5±10.9, respectively. The axSpA and AS groups did not differ in terms of any of these SPARCC scores.

Table III lists the r coefficients for the correlations between the SPARCC scores of the patients with nr-axSpA and AS and their disease activity scores, inflammatory markers, and bone markers. In the patients with nr-axSpA,ASDAS-ESR and ASDAS-CRP correlated significantly with the BME score and the total inflammatory score. ESR and CRP levels correlated significantly with the BME, deep BME, and total inflammatory scores. Unlike the patients with nr-axSpA, the SPARCC scores of the patients with AS did not correlate with any of the inflammatory markers or disease activity scores. However, sCTX-I

Table I. Demographic and clinical characteristics of the patients with non-radiographic axial spondyloarthritis and ankylosing spondylitis.

Characteristics n (%) or mean ± SD	Axial SpA (total group, n=81)	nr-axSpA (n=36)	AS (n=45)	p-value*
Male	66 (82)	29 (81)	37 (82)	1.000
Age, years	32 ± 12	30 ± 11	34 ± 13	0.131
Time from symptoms onset, years	5.6 ± 7.9	3.8 ± 4.9	7.0 ± 9.5	0.081
Time from diagnosis of AS, years	1.5 ± 3.0	1.5 ± 2.7	1.5 ± 3.2	0.996
Smoking, current	28 (35)	11 (31)	17 (38)	0.639
Family history of AS	11 (14)	6 (17)	5 (11)	0.526
HLA B27-positive	70 (86)	29 (81)	41 (91)	0.203
Patient global assessment score, 0–10	5.4 ± 2.1	5.3 ± 2.0	5.4 ± 2.2	0.981
Fatigue score, 0–10	5.8 ± 2.2	5.8 ± 2.3	5.9 ± 2.2	0.851
Spinal pain score, 0–10	5.8 ± 2.3	5.8 ± 2.4	5.8 ± 2.2	0.605
Pain and swelling of pph. joints score, 0–10	2.9 ± 2.9	2.6 ± 3.0	3.1 ± 2.7	0.426
Pain at entheseal sites score, 0–10	3.9 ± 2.9	3.8 ± 3.1	4.0 ± 2.7	0.825
Severity of morning stiffness score, 0–10	5.3 ± 2.9	5.5 ± 2.8	5.0 ± 3.1	0.509
Duration of morning stiffness score, 0–10	4.8 ± 3.7	5.6 ± 4.0	4.1 ± 3.4	0.080
BASDAI score, 0–10	4.7 ± 1.9	4.8 ± 1.9	4.6 ± 1.9	0.686
BASFI score, 0–10	2.3 ± 2.3	2.2 ± 2.3	2.4 ± 2.4	0.719
ASDAS-ESR	3.0 ± 1.0	2.9 ± 1.1	3.0 ± 1.0	0.618
ASDAS-CRP	2.7 ± 1.1	2.6 ± 1.0	2.8 ± 1.2	0.467
ESR, mm/hr	25.0 ± 23.2	21.2 ± 25.0	28.0 ± 21.4	0.012
CRP, mg/l	13.1 ± 20.1	9.7 ± 18.5	15.8 ± 22.0	0.087
BALP, U/l	27.8 ± 11.5	27.5 ± 8.4	28.1 ± 13.4	0.850
sCTX-I, ng/ml	0.44 ± 0.41	0.48 ± 0.56	0.41 ± 0.24	0.996
Grade of sacroiliitis on x-ray	2.1 ± 1.1	1.0 ± 0.5	2.9 ± 0.5	<0.001
mSASSS	5.4 ± 11.1	1.2 ± 5.2	8.8 ± 13.3	<0.001
Number of syndesmophytes	1.7 ± 4.0	0.3 ± 1.8	2.7 ± 4.9	<0.001
Receiving NSAIDs	78 (96)	35 (97)	43 (96)	1.000
Receiving sulfasalazine	30 (25)	9 (25)	11 (24)	1.000

AS: ankylosing spondylitis; ASDAS: Ankylosing Spondylitis Disease Activity Score; BALP: bone-specific alkaline phosphatase; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; mSASSS: modified Stokes Ankylosing Spondylitis Score; n: number; nr-axSpA: non-radiographic axial spondyloarthritis; NSAIDs: non-steroidal anti-inflammatory drugs; sCTX-I: serum C-terminal telopeptide of type-I collagen; SD: standard deviation.
*p-values were determined by comparing the AS and nr-axSpA groups using the Mann-Whitney U-test or Chi-squared test.

Table II. Acute inflammatory sacroiliac joint scores of the patients with non-radiographic axial spondyloarthritis and ankylosing spondylitis.

MRI score, mean ± SD	nr-axSpA (n=36)	AS (n=45)	p-value*
Acute inflammation			
Presence of bone marrow oedema, 0–48	7.0 ± 6.6	7.4 ± 9.1	0.845
Presence of deep bone marrow oedema, 0–12	1.4 ± 2.0	1.5 ± 2.2	0.798
Presence of intense bone marrow oedema, 0–12	0.7 ± 1.5	1.5 ± 2.2	0.451
Total inflammatory score, 0–72	9.1 ± 8.6	9.9 ± 12.5	0.734

AS: ankylosing spondylitis; MRI: magnetic resonance imaging; nr-axSpA: non-radiographic axial spondyloarthritis; SD: standard deviation.
The scores were determined by scoring the magnetic resonance images of the sacroiliac joints according to the SPondyloArthritis Research Consortium of Canada (SPARCC) method. Deep bone marrow oedema was defined as ≥1 cm. Intense bone marrow oedema was defined as being comparable to, or greater than, the appearance of blood in pre-sacral veins.
*p-values were determined by comparing the AS and nr-axSpA groups using the Mann-Whitney U-test.

Table III. Correlations between acute inflammatory scores of the sacroiliac joints of patients with non-radiographic axial spondyloarthritis and ankylosing spondylitis and disease activity scores, inflammatory markers, and markers of bone metabolism

	nr-axSpA (n=36)				AS (n=45)			
	BME	Deep BME	Intense BME	Total inflammatory score	BME	Deep BME	Intense BME	Total inflammatory score
PGA	0.116 (0.501)	0.052 (0.764)	-0.037 (0.829)	0.072 (0.678)	0.253 (0.093)	0.161 (0.290)	0.017 (0.758)	0.248 (0.100)
BASDAI	0.013 (0.941)	-0.031 (0.856)	0.004 (0.980)	0.001 (0.995)	0.077 (0.616)	0.112 (0.465)	-0.076 (0.618)	0.059 (0.698)
ASDAS-ESR	0.491 (0.002)	0.243 (0.154)	0.191 (0.263)	0.446 (0.006)	0.156 (0.306)	0.186 (0.220)	-0.030 (0.847)	0.145 (0.341)
ASDAS-CRP	0.485 (0.003)	0.371 (0.026)	0.174 (0.310)	0.453 (0.006)	0.180 (0.236)	0.192 (0.207)	-0.052 (0.733)	0.163 (0.285)
ESR, mm/hr	0.604 (<0.001)	0.385 (0.020)	0.293 (0.083)	0.576 (<0.001)	0.065 (0.671)	0.163 (0.286)	-0.001 (0.995)	0.066 (0.668)
CRP, mg/l	0.629 (<0.001)	0.512 (0.001)	0.293 (0.083)	0.606 (<0.001)	0.121 (0.430)	0.162 (0.288)	-0.081 (0.597)	0.098 (0.523)
BALP (U/l)	-0.029 (0.877)	0.012 (0.949)	0.088 (0.633)	0.006 (0.974)	0.082 (0.597)	0.138 (0.373)	-0.006 (0.968)	0.099 (0.522)
sCTX-I (ng/ml)	-0.012 (0.948)	0.104 (0.564)	-0.142 (0.430)	0.012 (0.948)	0.357 (0.018)	0.434 (0.003)	0.028 (0.066)	0.369 (0.014)

Results are shown as correlation coefficients (*p*-value), which were calculated using Spearman's correlation test.
The inflammation scores were determined by scoring the magnetic resonance images of the sacroiliac joints according to the SPondyloArthritis Research Consortium of Canada (SPARCC) method. Deep bone marrow oedema was defined as ≥1 cm. Intense bone marrow oedema was defined as being comparable to, or greater than, the appearance of blood in pre-sacral veins
AS: ankylosing spondylitis; ASDAS: Ankylosing Spondylitis Disease Activity Score; BALP: bone-specific alkaline phosphatase; BASDAI: Bath AS Disease Activity Index; BME: bone marrow oedema; nr-axSpA: non-radiographic axial spondyloarthritis; PGA: patient global assessment score; sCTX-I: serum C-terminal telopeptide of type-I collagen.

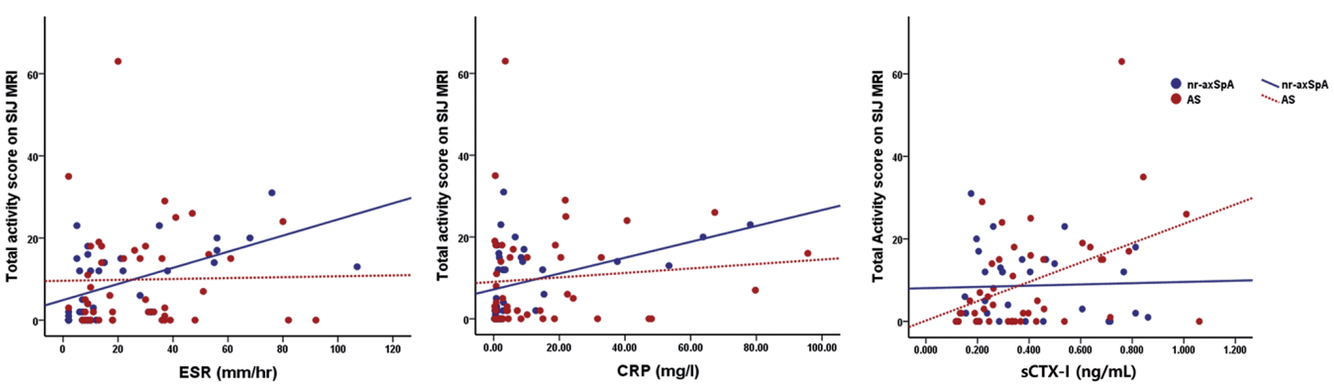

Fig. 1. Correlation between total inflammatory scores of patients with non-radiographic axial spondyloarthritis (nr-axSpA) and ankylosing spondylitis (AS) and (**A**) erythrocyte sedimentation rate (ESR), (**B**) C-reactive protein (CRP) levels, and (**C**) serum C-terminal telopeptide of type-I collagen (sCTX-I) levels. The total inflammatory scores were determined by scoring the magnetic resonance images of the sacroiliac joints according to the SPondyloArthritis Research Consortium of Canada (SPARCC) method. The total inflammatory score correlated with ESR and CRP in nr-axSpA (r=0.576, $p<0.001$ and r=0.606, $p<0.001$, respectively) but not in AS. sCTX-I correlated with total inflammatory score in AS only (r=0.369 and $p=0.014$).

levels correlated with the BME, deep BME, and total inflammatory scores, but not the intense BME score. The PGA, BASDAI, and BALP levels did not correlate with any of the MRI inflammatory scores in either group.

Figure 1 shows that ESR and CRP correlated significantly with total inflammatory SPARCC scores in nr-axSpA (r=0.576, $p<0.001$ and r=0.606, $p<0.001$, respectively) but not in AS. sCTX-I correlated with total inflammatory scores in AS (r=0.369, $p=0.014$) but not in nr-axSpA.

Of the 45 patients with AS, 11 (24%) had elevated sCTX-I levels (defined as >0.584 ng/ml in male patients ≤50 years old, >0.704 ng/ml in male patients >50 years old, and >0.573 in female patients). The patients with elevated sCTX-I levels had higher BME, deep BME, and total inflammatory SPARCC scores than the patients with normal sCTX-I levels (Table IV, $p=0.002$, 0.034, and 0.003, respectively).

Table V shows the results of univariate and multivariate linear analyses of the associations between total inflammatory SPARCC score and demographic, clinical, and laboratory variables in AS. Univariate analysis revealed that the total inflammatory score associated with age, symptom duration, severity of morning stiffness, and sCTX-I levels. However, multivariate analysis showed that only sCTX-I levels associated independently with total inflammatory score in AS (β=17.047 and $p=0.038$).

Discussion

In this study, we investigated the relationship between objective sacroiliitis, as measured by MRI, and disease activity scores, inflammatory markers, and bone markers in nr-axSpA and AS. We found that the variables that best reflected MRI-determined SIJ inflammation differed depending on the degree of radiographic sacroiliitis: inflammatory markers and ASDAS correlated with MRI sacroiliitis in patients with nr-axSpA only, whereas sCTX-I level was the only variable to correlate with MRI sacroiliitis in AS.

In routine practice, the disease activity in axSpA is usually assessed and monitored using patient self-reported measures (20). However, this approach

is limited by the fact that clinical variables do not reflect the histopathological inflammation at the site of disease. By contrast, MRI-detected inflammation in the SIJ correlates with the histopathological features. As a result, MRI inflammation was suggested as the best way to measure disease activity in axSpA (21). Moreover, inflammatory changes in the SIJ, as detected by MRI, have prognostic significance in radiographic sacroiliitis (22-24). In addition, chronic inflammatory lesions such as fat metaplasia, erosion, and ankylosis on SIJ MRI associate with spinal progression (25). These findings suggest that the inflammatory findings of SIJ MRI may help to predict radiographic changes. Several studies have also shown that MRI can help to monitor axSpA activity after TNF inhibitor treatment: MRI showed that this treatment improved the objective inflammatory lesions during follow-up (7, 8, 26). Thus, MRI of inflammatory lesions is not only helpful for diagnosing axSpA and monitoring its activity, but also provides information regarding later radiographic progression.

However, the clinical utility of MRI in axSpA is limited by restrictions in the availability and accessibility of MRI machines, the frequent restriction of the imaging to a single region, and the long time and high cost needed to acquire the sequences (27). To improve the management of axSpA, it would be useful to identify disease activity scores or laboratory biomarkers that accurately reflect MRI sacroiliitis. At present, several studies have investigated whether disease activity scores or laboratory markers reflect the objective inflammation measured by MRI. However, most were in patients who were treated with TNF inhibitors or had early axSpA (10-12, 26). Several studies showed that while MRI inflammation of the SIJ or spine did not correlate with BASDAI (14, 26), it did correlate with the new composite score ASDAS (12, 14, 26). With regard to the relationship between CRP and MRI inflammation, the results are inconsistent: although a few studies showed that CRP associated with MRI inflammation (14, 26, 28), this was not observed in other studies (12, 29).

Table IV. Acute inflammatory scores of the sacroiliac joints in ankylosing spondylitis patients who had normal or elevated levels of serum C-terminal telopeptide of type-I collagen.

	AS (n=45)		
	Normal sCTX-I (n=34)	Elevated sCTX-I (n=11)	*p*-value*
Presence of bone marrow oedema, 0–48	4.7 ± 5.7	15.6 ± 12.7	0.002
Presence of deep bone marrow oedema, 0–12	1.1 ± 2.0	2.7 ± 2.5	0.034
Presence of intense bone marrow oedema, 0–12	0.6 ± 1.3	2.2 ± 3.4	0.051
Total inflammatory score, 0–72	6.4 ± 8.2	20.6 ± 17.1	0.003

AS: ankylosing spondylitis; sCTX-I: serum C-terminal telopeptide of type-I collagen.
The scores were determined by scoring the magnetic resonance images of the sacroiliac joints according to the SPondyloArthritis Research Consortium of Canada (SPARCC) method. Deep bone marrow oedema was defined as ≥1 cm. Intense bone marrow oedema was defined as being comparable to, or greater than, the appearance of blood in pre-sacral veins.
*p-values were determined by comparing the AS and nr-axSpA groups using the Mann-Whitney U-test.

Table V. Univariate and multivariate linear regression analysis of the association of total inflammatory scores with demographic and clinical variables in patients with ankylosing spondylitis

Variables	Univariate analysis			Multivariate analysis		
	β	SE	*p*-value	β	SE	*p*-value
Age, years	-0.367	0.135	0.009	-0.159	0.162	0.332
Male sex	8.226	4.762	0.091			
Years after Sx. Onset, years	-0.434	0.192	0.029	-0.147	0.215	0.500
Disease duration, years	-0.235	0.592	0.693			
HLA B27-positive	-11.646	6.374	0.075			
Patient global assessment score, 0–10	1.337	0.838	0.118			
Fatigue score, 0–10	-0.809	0.869	0.357			
Spinal pain score, 0–10	0.716	0.847	0.403			
Pain and swelling of pph. joints score, 0–10	-0.673	0.656	0.310			
Pain at entheseal sites score, 0–10	0.160	0.695	0.819			
Severity of morning stiffness score, 0–10	1.236	0.582	0.040	0.659	0.579	0.262
Duration of morning stiffness score, 0–10	0.904	0.543	0.103			
BASDAI score, 0–10	0.351	1.002	0.728			
BASFI score, 0–10	-0.956	0.786	0.230			
ASDAS-ESR	1.742	1.842	0.350			
ASDAS-CRP	1.299	1.587	0.818			
ESR, mm/hr	0.011	0.089	0.903			
CRP, mg/l	0.055	0.086	0.530			
BALP, U/l	0.058	0.144	0.688			
sCTX-I, ng/ml	23.463	7.365	0.003	17.047	7.913	0.038
Grade of sacroiliitis on x-ray	2.970	3.481	0.398			
Number of syndesmophytes	-0.373	0.385	0.339			
				$R^2 = 0.529$		

β: unstandardised coefficients; SE: standard error; R^2: adjusted R square.
ASDAS: Ankylosing Spondylitis Disease Activity Score; BALP: bone-specific alkaline phosphatase; BASDAI: Bath AS Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; PGA: sCTX-I: serum C-terminal telopeptide of type-I collagen.
The total inflammatory scores were determined by scoring the magnetic resonance images of the sacroiliac joints according to the SPondyloArthritis Research Consortium of Canada (SPARCC) method.

These conflicting findings may reflect differences between the studies in terms of the baseline status of their cohorts. This is supported by a recent study that showed that CRP only correlated with MRI inflammation in patients with short disease duration: this association was not observed in patients with long-standing disease (13). This observation also indicates that the relationship between MRI inflammation and laboratory variables may change as the disease progresses. Indeed, the previous studies showed that while the inflammation and radiographic damage in AS is more extensive in AS than in nr-axSpA, the two groups do not differ in terms of BASDAI, PGA, or BASFI (30, 31).

This is the first study to investigate the influence of radiographic sacroiliitis on the correlation between activity scores, laboratory data, and inflammation on SIJ MRI. Indeed, we found that radiographic sacroiliitis does shape the biomarkers that reflect objective inflammation in axSpA, as measured by MRI. First, ESR, CRP, and ASDAS correlated with MRI-measured SIJ inflammation in nr-axSpA but not in AS. These correlations are consistent with a previous study on patients with early axSpA (14). Second, we found that sCTX-I levels associated with MRI-measured SIJ sacroiliitis in AS but not in nr-axSpA. None of the inflammatory markers and disease activity scores associated with MRI sacroiliitis in AS.

The observation that sCTX-I associates with MRI-measured SIJ sacroiliitis in AS is interesting. In axSpA, syndesmophytes and bamboo spine result from new bone formation, which is induced by chronic inflammation. Inflammatory cytokines, chemokines, and growth factors from immune cells can also activate osteoclasts, thereby causing periarticular osteopenia and systemic bone loss (32). These observations suggest that it would be useful to identify laboratory markers that reflect both bone turnover and inflammation and can predict bony change. Such markers would help to identify those patients with axSpA who would benefit most from aggressive treatment. One such marker may be sCTX-I. Patients with AS have higher CTX-I levels than healthy controls (33, 34), and it is well known that sCTX-I levels correlate negatively with bone mineral density in axSpA (33, 35, 36). Moreover, high sCTX-I levels associate with spinal radiographic damage in AS patients with active and longstanding disease (35); they are also an independent predictor of time to TNF inhibitor discontinuation and associate with disease activity in AS (37). Based on our results, sCTX-I may be useful as a biomarker that reflects both objective inflammation and bone turnover in AS. Its usefulness is further enhanced by the fact that it can be easily measured in samples from patients at different time points with relatively low cost. It should be noted that Pedersen *et al*. did not observe that sCTX-I levels in axSpA patients associated with the degree of MRI inflammation (38). However, this is likely to reflect the fact that the association was not assessed separately in nr-axSpA and AS. Nevertheless, the relationship between sCTX-I levels and MRI inflammation should be confirmed by further longitudinal studies.

Previous studies have shown that serum matrix metalloproteinase-3 (MMP-3) is a useful marker of disease activity in AS (39, 40). However, other study showed that MMP-3 levels do not correlate with inflammatory markers or BASDAI (41). Moreover, the changes in MMP-3 levels relative to baseline 12 weeks after TNF inhibitor treatment do not correlate with changes in MRI inflammation (42). Thus, it remains unclear whether MMP-3 is truly useful for assessing disease activity or serving as a measure of objective inflammation in AS.

Unlike MMP-3, CRP is thought to be useful in assessing disease activity, predicting the response to treatment, serving as a measure of the inflammation seen on MRI, and predicting radiographic progression. However, it suffers from poor sensitivity and specificity (43). Moreover, it does not correlate with MRI inflammation in longstanding axSpA (13). The present study also showed that it did not associate with sacroiliitis on MRI in AS.

This study has some limitations. First, it had a cross-sectional design, which means that the results should be interpreted with some caution. Longitudinal cohort studies are needed to confirm whether sCTX-I may be a useful marker of objective inflammation in SIJ in AS. Second, we did not assess spinal inflammation. The levels of serum markers could be influenced by spinal inflammation as well as by sacroiliac inflammation. Third, the sample size was relatively small, which could have reduced the statistical power of the study. The possibility that sCTX-I reflects MRI inflammation in AS should be confirmed by further prospective studies with larger cohorts.

In conclusion, this cross-sectional study showed that inflammatory markers and ASDAS correlated with active sacroiliitis on MRI in nr-axSpA, whereas only sCTX-I levels correlated with active inflammation on SIJ MRI in AS. Moreover, sCTX-I levels associated independently with the severity of the objective inflammation in SIJ in AS. These findings suggest that sCTX-I may be useful as a marker of objective inflammation in AS.

References

1. RUDWALEIT M, LANDEWÉ R, VAN DER HEIJDE D *et al*.: The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part I): classification of paper patients by expert opinion including uncertainty appraisal. *Ann Rheum Dis* 2009; 68: 770-6.
2. VAN DER LINDEN S, VALKENBURG HA, CATS A: Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum* 1984; 27: 361-8.
3. MAKSYMOWYCH WP: MRI and X-ray in axial spondyloarthritis: the relationship between inflammatory and structural changes. *Arthritis Res Ther* 2012; 14: 207.
4. RUDWALEIT M, VAN DER HEIJDE D, LANDEWÉ R *et al*.: The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. *Ann Rheum Dis* 2009; 68: 777-83.
5. GIOVANNINI L, ORLANDI M, LODATO C *et al*.: One year in review 2015: spondyloarthritis. *Clin Exp Rheumatol* 2015; 33: 769-78.
6. SIEPER J, RUDWALEIT M, BARALIAKOS X *et al*.: The Assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis. *Ann Rheum Dis* 2009; 68 Suppl. 2: ii1-44.
7. SIEPER J, VAN DER HEIJDE D, DOUGADOS M *et al*.: Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: results of a randomised placebo-controlled trial (ABILITY-1). *Ann Rheum Dis* 2013; 72: 815-22.
8. DOUGADOS M, VAN DER HEIJDE D, SIEPER J *et al*.: Symptomatic efficacy of etanercept and its effects on objective signs of inflammation in early nonradiographic axial spondyloarthritis: a multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheumatol* 2014; 66: 2091-102.
9. MAKSYMOWYCH WP: MRI in ankylosing spondylitis. *Curr Opin Rheumatol* 2009; 21: 313-7.
10. ALMODOVAR R, RIOS V, OCANA S *et al*.: Association of biomarkers of inflammation, cartilage and bone turnover with gender, disease activity, radiological damage and sacroiliitis by magnetic resonance imaging in patients with early spondyloarthritis. *Clin Rheumatol* 2014; 33: 237-41.
11. MACKAY JW, ABOELMAGD S, GAFFNEY JK: Correlation between clinical and MRI disease activity scores in axial spondyloarthritis. *Clin Rheumatol* 2015; 34: 1633-8.
12. PEDERSEN SJ, SORENSEN IJ, HERMANN KG *et al*.: Responsiveness of the Ankylosing

Spondylitis Disease Activity Score (ASDAS) and clinical and MRI measures of disease activity in a 1-year follow-up study of patients with axial spondyloarthritis treated with tumour necrosis factor alpha inhibitors. *Ann Rheum Dis* 2010; 69: 1065-71.
13. WEISS A, SONG IH, HAIBEL H, LISTING J, SIEPER J: Good correlation between changes in objective and subjective signs of inflammation in patients with short- but not long duration of axial spondyloarthritis treated with tumor necrosis factor-blockers. *Arthritis Res Ther* 2014; 16: R35.
14. NAVARRO-COMPAN V, RAMIRO S, LANDEWÉ R *et al*.: Disease activity is longitudinally related to sacroiliac inflammation on MRI in male patients with axial spondyloarthritis: 2-years of the DESIR cohort. *Ann Rheum Dis* 2016; 75: 874-8.
15. GARRETT S, JENKINSON T, KENNEDY LG, WHITELOCK H, GAISFORD P, CALIN A: A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. *J Rheumatol* 1994; 21: 2286-91.
16. VAN DER HEIJDE D, LIE E, KVIEN TK *et al*.: ASDAS, a highly discriminatory ASAS-endorsed disease activity score in patients with ankylosing spondylitis. *Ann Rheum Dis* 2009; 68: 1811-8.
17. CALIN A, GARRETT S, WHITELOCK H *et al*.: A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. *J Rheumatol* 1994; 21: 2281-5.
18. WANDERS AJ, LANDEWÉ RB, SPOORENBERG A *et al*.: What is the most appropriate radiologic scoring method for ankylosing spondylitis? A comparison of the available methods based on the Outcome Measures in Rheumatology Clinical Trials filter. *Arthritis Rheum* 2004; 50: 2622-32.
19. MAKSYMOWYCH WP, INMAN RD, SALONEN D *et al*.: Spondyloarthritis research Consortium of Canada magnetic resonance imaging index for assessment of sacroiliac joint inflammation in ankylosing spondylitis. *Arthritis Rheum* 2005; 53: 703-9.
20. CHE H, ETCHETO A, DERNIS E *et al*.: Evaluation of collected outcome measures in axial spondyloarthritis in daily-care rheumatology settings: the experience of the RHEVER network. *Clin Exp Rheumatol* 2015; 33: 851-7.
21. MAKSYMOWYCH WP: Biomarkers in axial spondyloarthritis. *Curr Opin Rheumatol* 2015; 27: 343-8.
22. BENNETT AN, MCGONAGLE D, O'CONNOR P *et al*.: Severity of baseline magnetic resonance imaging-evident sacroiliitis and HLA-B27 status in early inflammatory back pain predict radiographically evident ankylosing spondylitis at eight years. *Arthritis Rheum* 2008; 58: 3413-8.
23. BLUM U, BUITRAGO-TELLEZ C, MUNDINGER A *et al*.: Magnetic resonance imaging (MRI) for detection of active sacroiliitis--a prospective study comparing conventional radiography, scintigraphy, and contrast enhanced MRI. *J Rheumatol* 1996; 23: 2107-15.
24. OOSTVEEN J, PREVO R, DEN BOER J, VAN DE LAAR M: Early detection of sacroiliitis on magnetic resonance imaging and subsequent development of sacroiliitis on plain radiography. A prospective, longitudinal study. *J Rheumatol* 1999; 26: 1953-8.
25. KANG KY, KIM IJ, YOON MA, HONG YS, PARK SH, JU JH: Fat metaplasia on sacroiliac joint magnetic resonance imaging at baseline is associated with spinal radiographic progression in patients with axial spondyloarthritis. *PLoS One* 2015; 10: e0135206.
26. MACHADO P, LANDEWÉ RB, BRAUN J *et al*.: MRI inflammation and its relation with measures of clinical disease activity and different treatment responses in patients with ankylosing spondylitis treated with a tumour necrosis factor inhibitor. *Ann Rheum Dis* 2012; 71: 2002-5.
27. CHARY-VALCKENAERE I, D'AGOSTINO MA, LOEUILLE D: Role for imaging studies in ankylosing spondylitis. *Joint Bone Spine* 2011; 78: 138-43.
28. LAMBERT RG, SALONEN D, RAHMAN P *et al*.: Adalimumab significantly reduces both spinal and sacroiliac joint inflammation in patients with ankylosing spondylitis: a multicenter, randomized, double-blind, placebo-controlled study. *Arthritis Rheum* 2007; 56: 4005-14.
29. LUKAS C, BRAUN J, VAN DER HEIJDE D *et al*.: Scoring inflammatory activity of the spine by magnetic resonance imaging in ankylosing spondylitis: a multireader experiment. *J Rheumatol* 2007; 34: 862-70.
30. KILTZ U, BARALIAKOS X, KARAKOSTAS P *et al*.: Do patients with non-radiographic axial spondylarthritis differ from patients with ankylosing spondylitis? *Arthritis Care Res* (Hoboken) 2012; 64: 1415-22.
31. BRAUN J, BARALIAKOS X, KILTZ U: Non-radiographic axial spondyloarthritis: a classification or a diagnosis? *Clin Exp Rheumatol* 2016; 34 (Suppl. 95): S5-6.
32. DAVEY-RANASINGHE N, DEODHAR A: Osteoporosis and vertebral fractures in ankylosing spondylitis. *Curr Opin Rheumatol* 2013; 25: 509-16.
33. VOSSE D, LANDEWÉ R, GARNERO P, VAN DER HEIJDE D, VAN DER LINDEN S, GEUSENS P: Association of markers of bone- and cartilage-degradation with radiological changes at baseline and after 2 years follow-up in patients with ankylosing spondylitis. *Rheumatology* (Oxford) 2008; 47: 1219-22.
34. PARK MC, CHUNG SJ, PARK YB, LEE SK: Bone and cartilage turnover markers, bone mineral density, and radiographic damage in men with ankylosing spondylitis. *Yonsei Med J* 2008; 49: 288-94.
35. ARENDS S, SPOORENBERG A, EFDE M *et al*.: Higher bone turnover is related to spinal radiographic damage and low bone mineral density in ankylosing spondylitis patients with active disease: a cross-sectional analysis. *PLoS One* 2014; 9: e99685.
36. KANG KY, HONG YS, PARK SH, JU JH: Increased serum alkaline phosphatase levels correlate with high disease activity and low bone mineral density in patients with axial spondyloarthritis. *Semin Arthritis Rheum* 2015; 45: 202-7.
37. ARENDS S, SPOORENBERG A, HOUTMAN PM *et al*.: The effect of three years of TNFalpha blocking therapy on markers of bone turnover and their predictive value for treatment discontinuation in patients with ankylosing spondylitis: a prospective longitudinal observational cohort study. *Arthritis Res Ther* 2012; 14: R98.
38. PEDERSEN SJ, SORENSEN IJ, LAMBERT RG *et al*.: Radiographic progression is associated with resolution of systemic inflammation in patients with axial spondylarthritis treated with tumor necrosis factor alpha inhibitors: a study of radiographic progression, inflammation on magnetic resonance imaging, and circulating biomarkers of inflammation, angiogenesis, and cartilage and bone turnover. *Arthritis Rheum* 2011; 63: 3789-800.
39. YANG C, GU J, RIHL M *et al*.: Serum levels of matrix metalloproteinase 3 and macrophage colony-stimulating factor 1 correlate with disease activity in ankylosing spondylitis. *Arthritis Rheum* 2004; 51: 691-9.
40. CHEN CH, LIN KC, YU DT *et al*.: Serum matrix metalloproteinases and tissue inhibitors of metalloproteinases in ankylosing spondylitis: MMP-3 is a reproducibly sensitive and specific biomarker of disease activity. *Rheumatology* (Oxford) 2006; 45: 414-20.
41. APPEL H, JANSSEN L, LISTING J, HEYDRICH R, RUDWALEIT M, SIEPER J: Serum levels of biomarkers of bone and cartilage destruction and new bone formation in different cohorts of patients with axial spondyloarthritis with and without tumor necrosis factor-alpha blocker treatment. *Arthritis Res Ther* 2008; 10: R125.
42. MAKSYMOWYCH WP, RAHMAN P, SHOJANIA K *et al*.: Beneficial effects of adalimumab on biomarkers reflecting structural damage in patients with ankylosing spondylitis. J *Rheumatol* 2008; 35: 2030-7.
43. DANVE A, O'DELL J: The ongoing quest for biomarkers in Ankylosing Spondylitis. *Int J Rheum Dis* 2015; 18: 826-34.