Evaluating joint-space narrowing and cartilage loss in rheumatoid arthritis by using MRI

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Abstract

Introduction: Magnetic resonance imaging (MRI) has been shown to be superior to radiography (XR) for assessing synovitis, osteitis, and bone erosion in rheumatoid arthritis (RA), particularly in clinical trials. However, relatively little has been reported on the ability of MRI to evaluate articular cartilage loss, or joint-space narrowing (JSN), in the hands and wrists. In a previous study, we adapted the nine-point Genant-modified Sharp XR-JSN score for use with MRI (MRI-JSN). In this study, we compare MRI-JSN with XR-JSN by using images from two multicenter clinical trials.

Methods: Baseline XR and 1.5-Tesla MR images of one hand and wrist from each of 47 subjects with RA enrolled in one of two multicenter clinical trials were evaluated by using the XR-JSN and MRI-JSN methods by a single radiologist experienced in the two methods. Radiographs and MR images were read independently on different occasions.

Results: In total, 575 of 611 joints were compared (one metacarpophalangeal joint of the thumb and 35 proximal interphalangeal joints were outside the MRI field of view and could not be assessed). The 22 (47%) subjects showed JSN with both XR and MRI, and 25 (53%) subjects showed no JSN with either method. No subject showed JSN with only one or the other method. MRI showed high agreement with XR (intraclass correlation coefficient = 0.83). Sensitivity of MRI for JSN, by using XR as the gold standard, was 0.94; specificity was 0.91; accuracy was 0.91; positive predictive value was 0.64; and negative predictive value was 0.99.

Conclusions: This validation exercise suggests that MRI JSN scoring may offer a viable alternative to XR JSN scoring in multicenter clinical trials of RA. However, the relative longitudinal sensitivity of MRI to change and the ability to discriminate therapeutic effect on JSN were not evaluated in this study.

Introduction

The past decade has seen remarkable advances in structure-modifying treatment of rheumatoid arthritis (RA), with several effective therapies having been shown to slow or stop the progression of radiographic (XR) bone erosion and joint-space narrowing. However, many patients do not respond fully to these therapies, or experience side effects, so further development is still needed. One obstacle to progress in this regard is that clinical trials of putative new therapies are becoming harder to perform with XR. This is in part because the introduction of effective therapies has made pure placebo-controlled studies no longer ethical, necessitating a shift to add-on and active-comparator study designs [1], which exhibit slower progression and smaller differences between treatment arms, and therefore require longer observation periods and larger numbers of patients to achieve discriminative power. Additionally, early rescue treatment for patients showing poor response complicates interpretation of long-term study results and makes detecting structural change quickly even more important. These factors, along with the decreasing availability of RA patients appropriate for such studies, have increased the cost of clinical trials and threaten to impede progress in therapeutic development.

MRI has been shown to be more sensitive than XR for detecting bone erosion in patients with RA [2-9] and thus offers a potential solution to this problem. However, relatively little has been reported on the ability of MRI to evaluate cartilage loss or JSN in the hands and wrists of RA patients [4,8,10]. In a previous study [7], we adapted the Genant-modified Sharp XR scoring method [11] for use with MRI in the hand, wrist, and foot, and found...
MRI to have greater sensitivity to change for both bone erosion and JSN than did XR [7]. We and others have also shown MRI adaptations of the 5-point van der Heijde-Sharp XR-JSN score to be effective [4,8,10]. In this study, we examined the diagnostic accuracy of the 9-point MRI-JSN score [7] based on the corresponding 9-point XR-JSN score as a gold standard, by using images acquired from two multicenter clinical trials.

Materials and methods
In total, 47 subjects (77% women, mean age 46 years) with RA enrolled in one of two multicenter randomized, controlled trials (24 patients from IMPRESS (Impact of Rituximab on Magnetic Resonance Imaging Evidence of Synovitis and Bone Lesions in Patients With Moderate or Severe Rheumatoid Arthritis) and 23 patients from RA SCORE (A Study of MabThera (Rituximab) in Patients with Rheumatoid Arthritis and Inadequate Response to Methotrexate)) were included in this evaluation. All subjects had baseline XR and MRI of one hand and wrist by using standardized image-acquisition protocols, as described later. Both study protocols underwent institutional board review and received ethical approval, and all patients provided informed consent to participate in the studies.

MRI
One hand and wrist of each patient was imaged with a 1.5-T whole-body MRI scanner by using a commercial surface coil. Reproducible positioning was ensured with a specially designed acrylic hand frame. Pulse sequences included coronal, T1-weighted, three-dimensional (3D) gradient-echo with spectral fat suppression. Repetition time (TR) was 43 milliseconds, echo time (TE) was 12 milliseconds, the field of view was 120 mm, the matrix was 512 × 195, and the slice thickness was 1.5 mm, giving a voxel resolution of 234 μm × 625 μm × 1,500 μm. Only one excitation was averaged. Anatomic coverage extended from the distal radioulnar joint proximally to the proximal interphalangeal (PIP) joints distally, and included the entire thumb. The joints of the hands were scanned separately from those of the wrist.

Radiography
Each of the two hands/wrists and feet of every patient were radiographed separately on high-resolution 10-inch × 12 inch single-emulsion, single-screen film, by using standardized positioning with a template. Hands/wrists were exposed postero-anteriory, with the x-ray beam centered between the second and third metacarpophalangeal (MCP) joints and perpendicular to the cassette. Radiographs were digitized to a pixel size of 100 microns at 12-bits per pixel.

Image analysis
All radiographs were assessed for JSN by using the Genant-modified Sharp method, in which 13 locations involving 17 joints (interphalangeal (IP), 1; PIP, 2; PIP, 3; PIP, 4; PIP, 5; MCP, 1; MCP, 2; MCP, 3; MCP, 4; MCP, 5; carpometacarpal (CMC), 3 to 5 as a unit; capitate-lunate-scaphoid space as a unit; and radiocarpal space (scaphoid-radius and lunate-radius joints as a unit)) (Figure 1a) in each hand/wrist were scored on a 9-point scale ranging from 0 to 4 in increments of 0.5 [11]. The maximum XR-JSN score per patient was 52. All MR images were assessed for JSN by using the same 9-point scale (0, no cartilage loss or JSN; 0.5, equivocal cartilage loss or JSN; 1.0, minimal (< 10%) but definitive cartilage loss or JSN; 1.5, mild (10% to 25%) cartilage loss or JSN; 2.0, moderate cartilage loss or JSN (26% to 75%, including unilaterally denuded areas but no bilaterally denuded areas or bone-on-bone contact); 2.5, moderate-severe cartilage loss or JSN (> 75%, including focal denuding or focal bone-on-bone contact); 3.0, complete cartilage denuding or diffuse bone-on-bone contact; 3.5, partial ankylosis; 4.0, complete ankylosis) in 25 joints (IP 1, PIP 2, PIP 3, PIP 4, PIP 5, MCP 1, MCP 2, MCP 3, MCP 4, MCP 5, CMC 2, CMC 3, CMC 4, CMC 5, CMC 5).
Assessed). Twenty-two (47%) subjects showed JSN with MRI, whereas 25 (53%) showed no JSN. Twenty-seven (55%) subjects were outside the MRI field of view and could not be evaluated. Twenty-five (53%) subjects showed no JSN with either method. MRI detected 44 more joints with JSN than X-ray did, but missed two PIP joints with JSN on X-ray. Mean MRI-JSN score was 6.7 (SD, 11.7) for all 25 joints and 4.2 (SD, 6.4) for the 13 joints also evaluated with X-ray. Mean X-ray-JSN score for these 13 joints was 3.0 (SD, 5.3). No statistically significant difference was found between MRI-JSN and X-ray-JSN scores for these 13 joints.

Table 1 summarizes the findings on a per-joint basis. As can be seen, 89% of joints showed identical scores with MRI as with X-ray. MRI-JSN also showed high agreement with X-ray-JSN based on ICC (0.83).

Sensitivity of MRI for JSN, using X-ray as the gold standard, was 0.94; specificity was 0.91; accuracy was 0.91; positive predictive value was 0.64; and negative predictive value was 0.99. ROC curve analysis (Figure 5) showed MRI to be highly discriminative of X-ray JSN, as defined by the Genant-modified Sharp score. The number of JSN-positive patients did not increase when X-ray scores were added from the other hand and both feet, which had not been imaged with MRI, but which typically are included in clinical trials using X-ray. However, when eight additional hand/wrist joints assessed with MRI were considered, a total of 36 JSN-positive joints and one JSN-positive patient were added.

Discussion
In this validation exercise, MRI assessment of JSN in the hands and wrists of patients with RA provided the same results as did X-ray assessment of the same joints. MRI was both highly sensitive and specific for JSN that was demonstrable with X-ray. This suggests that MRI-JSN scoring may offer a viable alternative to X-ray-JSN scoring in multicenter clinical trials of RA. This is important because clinical trials with X-ray have become more costly and time consuming over the past decade. RA patients appropriate for clinical trials are increasingly difficult to recruit, and the switch to active comparator study designs has increased the number of patients and the observation time required to discriminate reliably the differences in change between treatment arms. The increased sensitivity of MRI for detecting bone erosions [2-9] should allow it to demonstrate structure-modifying treatment more quickly and with fewer patients than X-ray could. However, the MRI scoring method that has been used in most clinical trials thus far, the Outcome Measures in Rheumatology Clinical Trials RA MRI Score (OMERACT-RAMRIS) [13], did not include cartilage loss or JSN, and thus lacked the content validity of X-ray for structural joint damage. This was a significant limitation because bone erosion and cartilage loss do not always show the same pattern of response to therapy, as illustrated in the randomized, controlled trial of the inhibitor of the receptor for activated nuclear factor-κB (RANKL), denosumab, reported by Cohen et al. [9]. In that study, 227 patients with established RA were treated with either placebo plus methotrexate or one of two doses of denosumab plus methotrexate and followed up...
Figure 2  JSN depiction in wrist joints  Coronal fat-suppressed T₁-weighted gradient-echo image of wrist (A) shows sharp delineation of bone margins free of chemical-shift artifacts, thus allowing accurate determination of the joint-space widths, corresponding closely to those seen with XR in the same wrist (B). Note how clearly both MRI and XR show the radius-lunate and radius-scaphoid joint spaces (arrows) to be narrowed (JSN) relative to the other joints in the field of view. A JSN score of 2.0 was given to these joints independently on MRI and XR. MRI (A) additionally depicts the articular cartilage directly as high-signal tissue lining the articular cortices of the bones and showing sharp contrast with adjacent low-signal joint fluid on one side and low-signal articular bone and subcortical marrow fat on the other. As illustrated in this example, the interfaces between opposing cartilage surfaces, particularly in normal joints, often can be sharply delineated. Note that although the radius-lunate and radius-scaphoid joints are clearly narrowed on both MRI and XR, MRI further shows the cartilage to be only thinned on both sides of these joints, without complete denuding in any location. This important distinction cannot be determined with XR.

Figure 3  Joint-space narrowing (JSN) depiction in metacarpophalangeal (MCP) joint  Coronal, fat-suppressed, T₁-weighted gradient-echo image of MCP joints 2 through 5 (A), and corresponding XR image (B) show grade-2.0 JSN of MCP 3 (arrow) but normal joint-space width of MCP 2, 4, and 5. The proximal interphalangeal joints are out of the plane of section on the MR image shown, but were visible on more-palmar sections of the scan (not shown).
longitudinally with XR (erosion and JSN) and MRI (erosion only). Although both MRI and XR showed denosumab to have strong erosion-suppressing effects, XR showed denosumab to have no effect on preventing JSN. Had XR been excluded from the study, the lack of efficacy on this structural end point would not have been noticed.

Fortunately, MRI is well suited for imaging articular cartilage [14-18]. It depicts joint anatomy tomographically and therefore without projectional distortions that can mimic JSN on conventional XR, and MRI also is able to visualize the articular cartilage tissue directly, rather than only as a space between opposing articular cortices, as with XR. Moreover, MRI shows the same distribution of involvement of joints in the hands and wrists of patients with RA as does XR [19]. Fat-suppressed, T₁-weighted 3D gradient-echo scans, as were used in this study, have been shown to delineate articular cartilage accurately in various joints, including the MCPs [15], and is commercially available on all clinical MRI systems operating at a magnetic field strength of 1.0 T or higher. Systems operating at lower field strengths currently have difficulty with this technique because of limitations in spectral fat suppression or selective water excitation. Selective fat suppression or water excitation are important for increasing T₁ contrast between cartilage and adjacent joint fluid or subchondral bone (marrow fat) and for eliminating chemical-shift effects [16], which distort cartilage-bone interfaces and can simulate cartilage thinning and JSN. Increasing receiver bandwidth can reduce chemical shift, but this reduces the signal-to-noise ratio of the images and does not completely eliminate the problem. Fat-suppressed, T₁-weighted, 3D gradient-echo is also the most commonly used pulse sequence for evaluating bone erosion in multicenter randomized controlled trials of RA.

**Table 1 Number and percentage of joints showing correlation of MRI-joint-space narrowing (JSN) with XR-JSN**

| XR-JSN score | 0.0  | 0.5  | 1.0  | 1.5  | 2.0  | 2.5  | 3.0  | 3.5  | 4.0  | Total |
|--------------|------|------|------|------|------|------|------|------|------|-------|
| 0.0          | 449  | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 493   |
| 0.5          | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0     |
| 1.0          | 2    | 22   | 0    | 5    | 0    | 0    | 0    | 0    | 0    | 29    |
| 1.5          | 0    | 1    | 0    | 0    | 0    | 0    | 0    | 0    | 2    | 2     |
| 2.0          | 0    | 1    | 30   | 7    | 0    | 0    | 0    | 0    | 38   | 6/6   |
| 2.5          | 0    | 0    | 0    | 0    | 7    | 1    | 0    | 0    | 9    | 1/6   |
| 3.0          | 0    | 0    | 0    | 0    | 0    | 3    | 0    | 0    | 4    | 0/7   |
| 3.5          | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0     |
| 4.0          | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0    | 0     |
| Totals       | 451  | 0    | 56   | 48   | 14   | 6    | 2    | 0    | 575  | 100   |

Bold values indicate exact agreement between 9-point Genant-modified Sharp XR-JSN score MRI-JSN and XR-JSN.
cept [24], rituximab [25], and tocilizumab [26]. In contrast approval of structure-modifying therapies, including abata-
been used in multiple clinical trials to gain regulatory 
the Genant-modified Sharp XR-JSN score [11], which has 
opportunity to add at least the same sensitivity for detecting RA 
patients by one. Thus, MRI of one hand/wrist seems to 
JSN-positive joints by 36 and the number of JSN-positive 
joints included by MRI increased the number of 
this study. Conversely, adding data from the eight addi-
default than for XR, MRI protocols in most clinical-trial protocols. In this study, 35 (19%) of 
188 of PIP joints were not adequately covered and 
therefore excluded from analysis. Despite this limitation 
and the fact that images from two different multicenter 
clinical trials were pooled for this investigation, MRI-
JSN correlated strongly with XR-JSN, attesting to the 
robustness of the MRI-JSN method.

Because of the longer imaging time required for MRI 
than for XR, MRI protocols in most clinical trials include 
only one or two hand(s)/wrist(s) per patient, whereas XR 
protocols typically include both hands/wrists and feet. 
Despite this greater anatomic coverage of XR, however, 
adding XR data from the other hand/wrist and both feet 
did not increase the number of JSN-positive patients in 
this study. Conversely, adding data from the eight addi-
tional joints included by MRI increased the number of 
JSN-positive joints by 36 and the number of JSN-positive 
joints by one. Thus, MRI of one hand/wrist seems to 
offer at least the same sensitivity for detecting RA 
patients with JSN as does XR of both hands and feet.

The MRI-JSN score used this study was modeled after 
the Genant-modified Sharp XR-JSN score [11], which has 
been used in multiple clinical trials to gain regulatory 
approval of structure-modifying therapies, including abata-
cept [24], rituximab [25], and tocilizumab [26]. In contrast 
to the van der Heijde-Sharp JSN-XR score, which uses a 
5-point scale, ranging from 0 to 4 in increments of 1 [27], 
the Genant-modified Sharp XR-JSN score uses a 9-point 
scale, also ranging from 0 to 4, but in increments of 0.5. 
Both methods examine PIP 2, PIP 3, PIP 4, PIP 5, MCP 1, 
MCP 2, MCP 3, MCP 4, MCP 5, CMC 3, CMC 4, CMC 5, 
and the capitate-scaphoid and radius-scaphoid joints, but 
the Genant-modified Sharp method combines CMC 3 to 5 
into a single space and adds the IP 1, capitate-lunate, and 
radius-lunate joints. Direct comparisons of these two XR 
scoring methods by using images from multicenter clinical 
trials, found that despite the differences in scales and spe-
cific joints examined by each, both methods showed the 
same discriminative power for XR-JSN change over time 
and between treatment arms [28,29].

The advantage of a 9-point scale over a 5-point scale is 
that including smaller increments across a similar range of 
structural damage may improve sensitivity to change, 
although comparative longitudinal studies are needed to 
evaluate this directly. Additionally, all images in this study 
were evaluated by a single, expert radiologist with 20 years 
of experience reading XR and MR images in RA clinical 
trials. As such, the results represent a best-case scenario 
and may not generalize to analyses performed by less-
experienced readers. Interreader variability and smallest 
detectable change were not evaluated. Time required to 
perform MRI-JSN scoring also was not evaluated; how-
ever, because the technique is extremely detailed, it may 
be time consuming for inexperienced readers to perform. 
In a previous investigation [7], we demonstrated the 9-
point MRI-JSN scale to be more sensitive to change than 
was the 9-point XR-JSN scale. We and others similarly 
found high interreader agreement and strong XR correla-
tion of a 5-point MRI-JSN score that was similar to the 
van der Heijde XR-JSN score [4,8,10]. McQueen et al. [4] 
recently compared MRI with XR by using such a 5-point 
scale in the wrists of 38 patients with RA and 22 control 
subjects by using 2D spin-echo and 3D gradient-echo MRI 
at 3 T but without fat suppression, except on postcontrast 
3D scans. Although chemical-shift artifacts are greater at 3 
T than at 1.5 T, and the joints evaluated by MRI and XR 
in their study were not exactly the same as those included 
in either modified-Sharp XR method, correlations were 
high between the total MRI cartilage score in the wrist 
and total XR-JSN score in the same wrist (0.61 to 0.74) or 
in both hands, wrists, and feet (0.68 to 0.78). A subsequent 
study by Ostergaard et al. [10] similarly found strong cor-
relation between a similar 5-point MRI-JSN scale and the 
van der Heijde-modified Sharp XR-JSN scale in the same 
hand and wrist.

Conclusions

When MRI and XR images were scored for JSN in the 
same 13 joint locations that are typically scored in XR
clinical trials of RA, the results agreed very well, with no statistically significant difference. Additional XR JSN scores in the feet and in the hand/wrist not imaged with MRI did not increase the number of JSN-positive patients, whereas the additional joints scored by using MRI increased involved joints and JSN-positive patient assignment. This suggests that MRI-JSN scoring may offer a viable alternative to XR-JSN scoring in multicenter clinical trials of RA. Replacement of XR with MRI in clinical studies of RA would allow longitudinal study designs to take advantage of the MRI improved ability to visualize erosion progression. The MRI relative longitudinal sensitivity to change and its ability to discriminate therapeutic effects specifically on JSN must be evaluated directly in coming studies.

**Abbreviations**

CMC: carpometacarpal; ICC: intraclass correlation coefficient; JSN: joint-space narrowing; MCP: metacarpophalangeal; MRI: magnetic resonance imaging; PIP: proximal interphalangeal; RA: rheumatoid arthritis; RANKL: receptor activator of NF-κB ligand; ROC: receiver operating characteristic; T: Tesla; T1: longitudinal magnetic spin relaxation time; X: X-ray.

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**Authors' contributions**

CP participated in protocol and experimental design, radiologic analysis, and drafted the manuscript. JD participated in protocol design, imaging acquisition and analysis of the reading results, and helped draft the manuscript. EO participated in protocol design, imaging acquisition, and reading results analysis. M-AB participated in protocol design, imaging acquisition, and reading results analysis. NG participated in protocol design, imaging acquisition, and reading results analysis. All authors read and approved the final manuscript.

**Competing interests**

CGP is a shareholder in Spire Sciences, and a consultant for Abbott, Amgen, AstraZeneca, Biogen-Idec, Bristol Myers-Squibb, Bioclinica, Celgene, Centocor, Core Lab Partners, Crescendo, Eli Lilly and Company, Genentech, Genzyme, Merck, Ikon Medical Imaging, Novartis, Perceptive Informatics, Pfizer, Rigel, Roche, UCBB, Wyeth, an employee of Spire Sciences, and a past employee of Synarc. JCDiC is a consultant for Abbott, Amgen, AstraZeneca, Biogen-Idec, Bristol Myers-Squibb, Bioclinica, Celgene, Centocor, Core Lab Partners, Crescendo, Eli Lilly and Company, Genentech, Genzyme, Merck, Ikon Medical Imaging, Novartis, Perceptive Informatics, Pfizer, Rigel, Roche, UCBB, and Wyeth, an employee of Spire Sciences, and a past employee of Synarc. JD participated in protocol and experimental design, radiologic analysis, and reading results analysis. All authors read and approved the final manuscript.

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