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# Chapter 3

Aiming for a simpler early arthritis MRI  
protocol: can Gd contrast administration be  
eliminated?

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## **ABSTRACT**

### **PURPOSE**

To evaluate whether intravenous gadolinium (Gd) contrast administration can be eliminated when evaluating synovitis and tenosynovitis in early arthritis patients, thereby decreasing imaging time, cost and invasiveness.

### **MATERIALS AND METHODS**

Wrist MRIs of 93 early arthritis patients were evaluated by two readers for synovitis of the radio-ulnar, radio-carpal and intercarpal joints, according to the Rheumatoid Arthritis MRI Scoring method (RAMRIS), and for tenosynovitis in ten compartments. Scores of MRI-images without Gd-contrast-enhancement were compared to scores obtained when evaluating all, including contrast-enhanced, MRI-images as reference. Subsequently a literature review and pooled analysis of data from the present and two previous studies were performed.

### **RESULTS**

At individual joint/tendon level, sensitivity to detect synovitis without Gd-contrast was 91% and 72% for the two readers, respectively, and specificity 51% and 81%. For tenosynovitis sensitivity was 67% and 54%, respectively and specificity 87% and 91%. Pooled data analysis revealed an overall sensitivity of 81% and specificity of 50% for evaluation of synovitis. Variations in tenosynovitis scoring systems hindered pooled analyses.

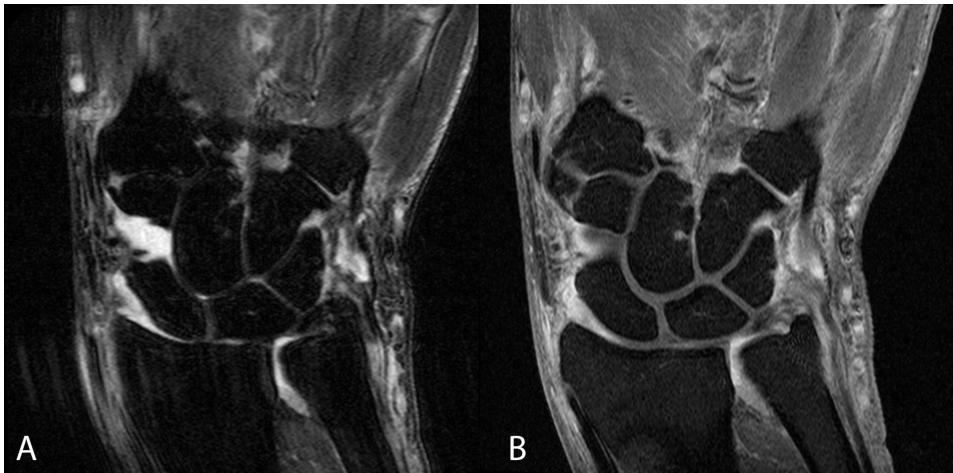
### **CONCLUSION**

Eliminating Gd contrast administration resulted in low specificity for synovitis and low sensitivity for tenosynovitis, indicating that Gd-contrast administration remains essential for an optimal assessment.

## INTRODUCTION

Magnetic Resonance Imaging (MRI) is increasingly used in research of Rheumatoid Arthritis (RA) and in clinical practice. MRI has high sensitivity to depict local inflammation in the form of synovitis, tenosynovitis and bone marrow edema.[1] The MRI protocol is standardized in the Outcome Measures in Rheumatology (OMERACT) Rheumatoid Arthritis MRI scoring (RAMRIS) method, which is a standardized scoring system for the assessment of synovitis, bone marrow edema and erosions.[2] OMERACT recommended MRI sequences include non contrast enhanced T1 weighted images which are primarily used to assess erosions, T2 weighted fat saturated images (T2) or short tau inversion recovery (STIR) images to evaluate bone marrow edema [2], and post-gadolinium (Gd) contrast T1-weighted images (T1Gd) used in combination with non-contrast T1 weighted images for evaluation of synovitis and tenosynovitis.[2–4]

The use of intravenous Gd contrast has drawbacks; it is an invasive procedure, carries a small risk of nephrogenic systemic fibrosis, it is costly and it prolongs the required imaging time. When Gd-contrast administration could be eliminated this would make MRI more patient-friendly and would increase accessibility. We hypothesized that, based on the high signal intensity of both synovitis and tenosynovitis on T2 and T1Gd images (illustrated in Figure 1), and despite the high signal intensity of synovium and fluid, it is possible to evaluate synovitis and tenosynovitis on T2 instead of T1Gd.



**Figure 1.** Example of synovitis as visualized by T2-weighted and T1-weighted postcontrast sequences. (a) T2-weighted coronal image before Gd administration and (b) corresponding T1-weighted coronal image after Gd administration. Synovitis of the radioulnar, radiocarpal and intercarpal joints is clearly visible on both sequences.

The objective of this study was to determine whether Gd contrast administration could be eliminated from the MRI protocol when assessing synovitis and tenosynovitis. This was achieved by a study of 93 early arthritis patients, a literature review and an analysis of pooled data from the current study and two previous studies.

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## MATERIALS AND METHODS

### PATIENTS

Between July 2011 and April 2012 MRI was performed in 93 early arthritis patients at the first visit of the hospital's Early Arthritis Clinic. The Early Arthritis Clinic is a population-based inception cohort that includes patients with confirmed arthritis and symptoms for <2 years.[5] These patients were part of a larger group in whom MRI was performed and results on which have been previously reported[1, 6, 7]; the current study concerns a subgroup of consecutive patients in which an extra axial T2-weighted sequence of the wrist was obtained. All patients provided informed consent and the study was approved by the institutional review board.

### MRI

MRI of the wrist was performed within two weeks after inclusion, of the most painful side, or in case of completely symmetric symptoms of the dominant side. The presence of clinical arthritis at physical examination of the wrist was not a prerequisite. MRI was performed on an MSK-extreme 1.5T extremity MRI system (GE, Wisconsin, USA) using a 100mm quadrature volume transmit and receive coil. The patient was positioned in a chair beside the scanner, with the hand fixed in the coil with cushions.

The following sequences were acquired before contrast administration: T1-weighted FSE sequence in the coronal plane (TR/TE 650/17ms; acquisition matrix 388×88; ETL2); T2-weighted FSE sequence with frequency selective fat saturation in the coronal and axial plane (TR/TE 3000/61.8ms; acquisition matrix, 300×224, ETL7). After intravenous administration of Gd contrast (gadoteric acid, Guerbet, Paris, France, standard dose of 0.1 mmol/kg) the following sequences were obtained: T1-weighted FSE sequence with frequency selective fat saturation in the coronal plane (TR/TE 650/17ms, acquisition matrix 364×224, ETL2), T1-weighted FSE sequence with frequency selective fat saturation in the axial plane (TR/TE 570/7ms; acquisition matrix 320×192; ETL2). Field-of-view was 100mm. Coronal sequences had 18 slices with a slice thickness of 2mm and a slice gap of 0.2mm. All axial sequences had 20 slices with a slice thickness of 3mm and a slice gap of 0.3mm. Total imaging time was approximately 25 minutes.

The MRIs were scored by two readers independently (research fellows with two and three years respectively of experience with RA MRI assessment), blinded to clinical data. Previously documented within-reader intraclass correlation coefficients for the total RAMRIS score were 0.98 and 0.83; and between-reader interclass correlation coefficient was 0.82. [1] All datasets were scored twice, one time using all acquired images (Gdset), and another time using only unenhanced images (T2set). The order of examinations was randomized between assessments and there was an interval of at least two months between assessments. Images were scored for synovitis according to RAMRIS on a 0-3 scale for the radio-ulnar, radio-carpal and the combined intercarpal and carpometacarpal joints.[2] Tenosynovitis was evaluated in 10 tendons/compartments on a 0-3 scale as described by Haavardsholm et al.[4]

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## LITERATURE REVIEW AND POOLED DATA ANALYSIS

For the literature review PubMed was searched with a broad search strategy using the search term (“gadolinium” OR “contrast” OR “enhancement”) AND (“synovitis” OR “arthritis” OR “tenosynovitis”) AND (“MRI” OR “MR” OR “magnetic resonance”). Available literature up to November 2013 was searched. This yielded 1035 results. Abstracts were screened and we selected studies that reported on findings on Gd contrast-enhanced images compared to findings on images obtained without Gd contrast in MRI of joints of the hand of adult patients with any type of arthritis. For relevant studies (n=3) full-text articles were obtained. Furthermore, references of obtained full-text articles were screened for further relevant studies, which did not yield any additional studies. Of the three studies that were found, two were relevant for synovitis and one for tenosynovitis.

For synovitis we performed a pooled data analysis; raw data were obtained from the literature [8] or obtained via personal communication [9] and combined to determine overall test characteristics. For tenosynovitis, due to different scoring systems used we could not perform a pooled data analysis.

## REFERENCE STANDARD AND STATISTICS

Gd-enhanced image scores were the reference standard. Comparisons were made for the two readers independently. To determine whether the same absolute scores were obtained by both methods, scores were compared with weighted kappa statistic and intraclass correlation coefficient (ICC) for absolute agreement. Bland-Altman plots were used to visualize the level of agreement. Furthermore, the sensitivity and specificity were calculated at both joint/tendon level (with results combined for all assessed joints/tendons) and at patient level (total synovitis and tenosynovitis scores), with scores  $\geq 1$  considered positive at both joint/tendon and patient level.

## RESULTS

Data from 92 patients were analyzed, as one MRI was excluded because of severe artifacts caused by a metallic foreign body. Patient characteristics are listed in Table 1. Both readers were able to assess all joints using both image sets. Based on reader 1 scores for Gdset (the reference standard) MRI synovitis was present in 162 joints (59%) and 81 patients (88%); tenosynovitis was present in 153 tendon compartments (17%) and 52 patients (57%).

## AGREEMENT FOR TOTAL SYNOVITIS AND TENOSYNOVITIS SCORES

For total scores within each patient, Bland-Altman plots showed acceptable levels of agreement (Figure 2). For tenosynovitis there was a tendency towards more variation with higher scores (heteroscedasticity) especially for reader 2. There was little systematic bias for both readers between the sets with and without Gd contrast, reader 1 had slightly higher

**Table 1.** Patient characteristics.

	Patients (n=92)
Age, years (mean, SD)	55.8 ±13.5
Female sex, n (%)	49 (53.3)
Symptom duration in weeks, median (IQR)	13.0 (4.8-29.0)
Swollen joint count (66-SJC), median (IQR)	3.0 (2.0-5.8)
Tender joint count (68-TJC), median (IQR)	6.5 (2.3-10.0)
RF positive, n (%)	28 (30.4)
ACPA positive, n (%)	23 (25.0)
Patient classification at baseline, n (%)	
RA (2010 criteria)	35 (38.0)
Undifferentiated arthritis	36 (39.1)
Inflammatory osteoarthritis	6 (6.5)
Psoriatic arthritis	7 (7.6)
Other rheumatic diagnoses	8 (8.7)

Except where indicated otherwise, values are number (%) of patients. SD, standard deviation; IQR, interquartile range; 66-SJC, 66 swollen joint count; 68-TJC, 68 tender joint count; RF, Rheumatoid factor; ACPA, anti-citrullinated peptide antibodies.

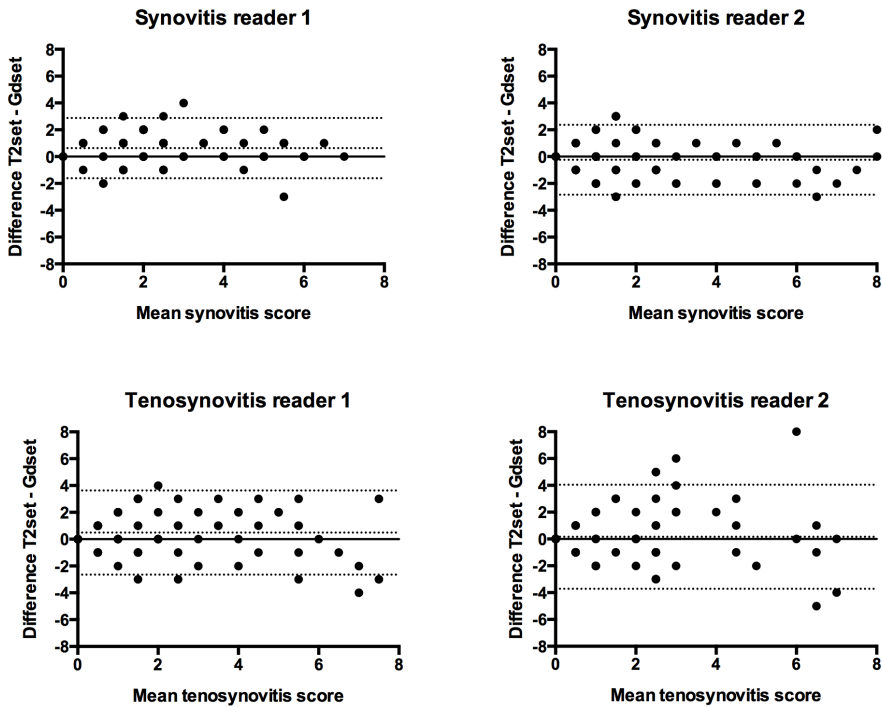
scores on the T2set, while reader 2 had virtually zero difference on average. ICCs between the T2set (without contrast) and Gdset (with Gd contrast) images were 0.75 (95%CI 0.54-0.86) and 0.82 (95%CI 0.74-0.88) for synovitis for the two readers, respectively and 0.72 (95%CI 0.60-0.81) and 0.57 (95%CI 0.42-0.70) for tenosynovitis, indicating moderate to good agreement for total synovitis and tenosynovitis scores.

### TEST CHARACTERISTICS ON PATIENT LEVEL

When evaluating the presence of synovitis at patient level without Gd contrast (the T2set), the sensitivity was 96% and 78%, respectively, for the two readers and the specificity was 36% and 71%. When tenosynovitis was assessed using the T2set the sensitivity was 89% and 71% and the specificity 40% and 68% (Table 2).

### AGREEMENT FOR INDIVIDUAL JOINT/TENDON SCORES

Subsequent analyses were performed on joint level with Gdset images as reference. Weighted Kappa's for agreement of synovitis scores in individual joints based on T2set and Gdset were 0.65 (95%CI 0.49-0.81) and 0.71 (95%CI 0.63-0.80) for the two readers, indicating good agreement. For tenosynovitis corresponding values were 0.52 (95%CI 0.36-0.68) and 0.46 (95%CI 0.33-0.60), indicating moderate agreement.



**Figure 2.** Bland-Altman plots of assessment of synovitis and tenosynovitis with and without Gd enhancement. Plots for total scores for synovitis (upper row) and tenosynovitis (lower row) for reader 1 (left) and reader 2 (right). The differences (T2set - Gdset) between paired measurements are plotted against the means of the two measurements. The middle line in each graph shows the systematic bias between the two measurement methods. The observation that the line is located around 0 indicates that systematic bias was low. The upper and lower lines show the  $\pm$  95% limits of agreement. For tenosynovitis variation increases with higher scores for reader 2.

### TEST CHARACTERISTICS ON JOINT/TENDON LEVEL

The sensitivity to detect synovitis without Gd contrast was 91% and 72%, respectively, for the 2 readers and the specificity 51% and 81%. Similarly, for tenosynovitis the sensitivity was 67% and 54% and the specificity 87% and 91% for the two readers (Table 2).

### LARGE DISCREPANCIES IN SCORES IN INDIVIDUAL JOINTS/TENDONS

Differences of  $>1$  point between T2set and Gdset scores in individual joints or tendons were present in only 1.8% of joints for synovitis and 0.3-0.5% of tendons for tenosynovitis. These cases were reviewed for the cause of this discrepancy. For synovitis, in all cases areas of high signal on T2 showed no enhancement on T1Gd images, indicating false-positive results on T2 due to effusion (Figure 3). For tenosynovitis no clear explanation was found.

**Table 2.** 2x2-table, and sensitivity and specificity of assessment of synovitis and tenosynovitis at joint/tendon level and at patient level without Gd contrast administration, with contrast enhanced MRI findings as standard reference.

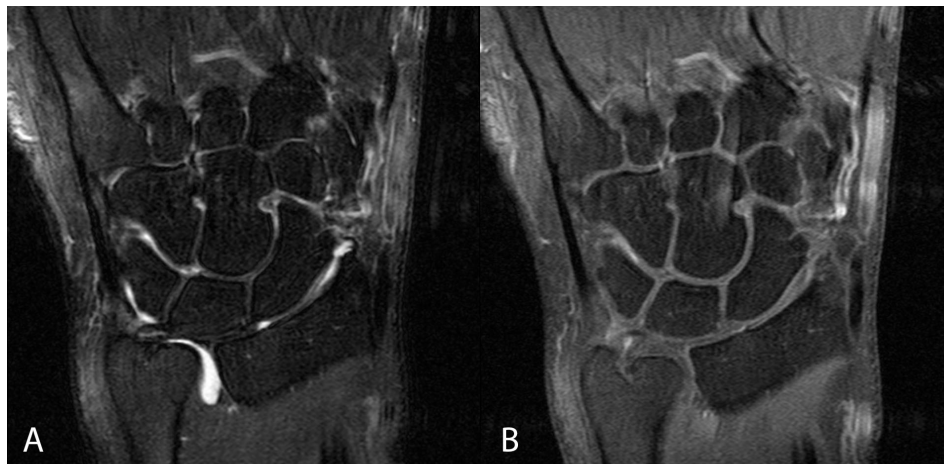
At joint/tendon level					
Synovitis Reader 1	Gdset+	Gdset-	Synovitis Reader 2	Gdset+	Gdset-
T2set+	148	56	T2set+	90	29
T2set-	14	58	T2set-	35	122
Sensitivity	91%		Sensitivity	72%	
Specificity	51%		Specificity	81%	
Tenosynovitis Reader 1	Gdset+	Gdset-	Tenosynovitis Reader 2	Gdset+	Gdset-
T2set+	103	97	T2set+	73	74
T2set-	50	670	T2set-	62	711
Sensitivity	67%		Sensitivity	54%	
Specificity	87%		Specificity	91%	
At patient level					
Synovitis Reader 1	Gdset+	Gdset-	Synovitis Reader 2	Gdset+	Gdset-
T2set+	78	7	T2set+	45	10
T2set-	3	4	T2set-	13	24
Sensitivity	96%		Sensitivity	78%	
Specificity	36%		Specificity	71%	
Tenosynovitis Reader 1	Gdset+	Gdset-	Tenosynovitis Reader 2	Gdset+	Gdset-
T2set+	46	24	T2set+	37	13
T2set-	6	16	T2set-	15	27
Sensitivity	89%		Sensitivity	71%	
Specificity	40%		Specificity	68%	

Presence of synovitis and tenosynovitis in individual joints and tendons and in patients with (Gdset) and without (T2set) Gd contrast. Synovitis was evaluated in 276 sites (three wrist joints in 92 patients) and tenosynovitis was evaluated in 920 sites (10 wrist compartments in 92 patients) as described in the methods.

**Table 3.** Overview of literature regarding the need of Gd contrast for assessment of synovitis and tenosynovitis.

Study	Patient group	MR	Joint area	Scoring method	Disease duration (mean/median)	ICC Gd+ vs Gd-	Sensitivity / specificity	Conclusion
Synovitis								
Ostergaard 2009	RA (n=40)	1.0/1.5T	10 wrist/ 30 mcp	RAMRIS	Unspecified	0.63-0.76	86-90% / 31-79%	Omitting IV contrast decreases reliability of synovitis scores
Tamai 2012	RA (n=45) healthy (n=9) Early RA (n=51)	0.2T Extremity 1.5T	Wrist and mcp Wrist, mcp and pip	RAMRIS RAMRIS	Unspecified 5 months	0.61 -	60% / 96% 78% / 50%	Synovitis cannot be correctly identified by plain MRI
Current study	Early arthritis (n=92)	1.5T Extremity	Wrist	RAMRIS	First patient visit	0.75-0.82	77-96% / 36-69%	
Tenosynovitis								
Tehranzadeh 2006	Inflammatory arthritis (n=30, 72 exams, RA 16, UA 9, PsA 2, CREST 1, SLE 1, paraneoplastic 1)	1.5T	33 wrist/ 39 hand	Self-devised, 0-3	Unspecified	-	40-67% / -	Enhanced MR imaging superior for detection of tenosynovitis.
Current study	Early arthritis (n=92)	1.5T Extremity	Wrist	RAMRIS	First patient visit	0.57-0.72	71-88% / 40-68%	

All relevant studies found evaluating findings on MRI with compared with MRI without Gd contrast administration; current study results also shown. Sensitivity and specificity shown are those reported for individual joints/tendons.



**Figure 3.** Example of large discrepancy in synovitis score between T1-weighted postcontrast and T2-weighted sequences. (a) T2-weighted coronal image before Gd administration and (b) corresponding T1-weighted coronal image after Gd administration. Effusion in the radioulnar and radiocarpal joints results in high signal on T2-weighted images without enhancement on post-Gd images.

#### LITERATURE REVIEW AND POOLED DATA ANALYSIS

Table 3 lists all studies that were identified and results of each individual study; two studies evaluated synovitis and one other study assessed tenosynovitis with and without contrast. [8–10] The tendency of the findings on joint/tendon level was consistent across studies: low specificity for synovitis; low sensitivity for tenosynovitis. The only exception was assessment of synovitis at 0.2T extremity MRI (as compared to 1.0 or 1.5T for other studies), where the sensitivity was low.[9] Figure 4 shows the sensitivity and specificity for synovitis obtained with 1.0/1.5T MRI in different studies. For synovitis, raw data of three studies were pooled on joint level; the overall sensitivity to detect synovitis without Gd was 81% and the overall specificity 50% (Figure 4, Table 4). For tenosynovitis pooling could not be performed due to differences in the scoring methods used.

#### DISCUSSION

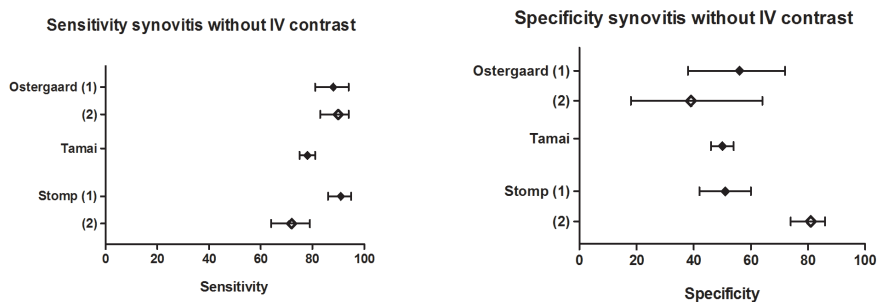
MRI is sensitive to detect inflammation, but is also time-consuming and costly. We investigated the consequences of eliminating Gd contrast administration for MRI of the wrist in a cohort of early arthritis patients and subsequently analyzed pooled data from this study and two previously published studies, identified by a literature review. We observed that the sensitivity and specificity were markedly decreased when eliminating the post-Gd contrast sequences.

Gd administration adds to the cost and duration of the examination and increases patient discomfort. Furthermore it is contraindicated in patients with severe renal failure due to the risk of nephrogenic systemic fibrosis.[11] For assessment of bone marrow edema and erosions no Gd contrast is necessary.[8, 9] However, based on our findings and the literature review, Gd contrast is necessary for optimal assessment of synovitis and tenosynovitis. Agreement for total synovitis and tenosynovitis scores, as tested by Bland-Altman plots and

**Table 4.** Pooled data from literature for synovitis: 2x2-table, and sensitivity and specificity of assessment of synovitis at joint level without Gd contrast administration, with contrast enhanced MRI findings as standard reference.

Ostergaard et al.	Gdset+	Gdset-	Total	
T2set+	101	16	117	PPV: 86%
T2set-	13	20	33	NPV: 61%
Total	114	36	150	
	Sensitivity: 89%	Specificity: 56%		
Tamai et al.	Gdset+	Gdset-	Total	
T2set+	613	316	929	PPV: 66%
T2set-	175	312	487	NPV: 64%
Total	788	628	1416	
	Sensitivity: 78%	Specificity: 50%		
Pooled data from Ostergaard et al and Tamai et al. and the current study	Gdset+	Gdset-	Total	
T2set+	862	388	1250	PPV: 69%
T2set-	202	390	592	NPV: 66%
Total	1064	778	1842	
	Sensitivity: 81%	Specificity: 50%		

Number of joints scored positive on T2set and Gdset; data from two other studies and pooled data from the present study as well as studies by Østergaard et al and Tamai et al.[5, 6] For studies that reported data on multiple readers, only scores of one reader were used (results were comparable independent of the combination of readers selected). PPV: positive predictive value; NPV: negative predictive value.



**Figure 4.** Sensitivity and specificity of evaluation of synovitis without Gd contrast in separate studies. Plot of sensitivity and specificity estimates for individual joints and tendons. (A) Sensitivity and (B) specificity. Point estimates of sensitivity and specificity from each study are shown as solid diamonds for the first reader and as open diamonds for the second reader in each study. The solid lines represent 95% CIs.

ICCs, was moderate to good with little systemic bias. Therefore when only total inflammation burden within the whole imaged area is of interest, a reasonably good indication may be obtained even without Gd contrast. However, test characteristics were unacceptably low to determine the presence of inflammation either on patient or individual joint/tendon level, and therefore in most practical situations Gd contrast administration cannot be eliminated.

An important advantage of using Gd contrast is the ability to differentiate between effusion and inflammation. In our population this was apparent when we reviewed the largest discrepancies in scores, which for synovitis were all in joints with evident effusion. This was an uncommon occurrence however in these early arthritis patients. Nevertheless, even small, physiologic, amounts of joint fluid may have given the false appearance of synovitis on T2 images, negatively affecting specificity. In patients with more advanced disease, this might pose a bigger problem, as effusion is more prevalent in these patients, thus we expect reliability without Gd contrast in these patients to be even lower.

In juvenile idiopathic arthritis patients who underwent knee MRI, omitting Gd contrast administration decreased the reliability of synovial hypertrophy scores.[12] Sensitivity rather than specificity was mainly affected; a possible explanation might be the more common occurrence of joint effusion in the knee, from which synovitis is difficult to differentiate without contrast enhancement. Likewise, in patients with knee osteoarthritis, MRI adequately assessed effusion volume but did not adequately detect synovitis.[13]

Although our results show that Gd contrast enhanced sequences cannot be simply left out of the MRI protocol, there might still be alternative options to avoid Gd contrast administration. The most promising option might be using diffusion-weighted imaging (DWI), which has successfully been applied in RA in a few small-scale studies.[14, 15] More advanced imaging with arterial spin-labeling could potentially even accurately quantify inflammation without using Gd contrast.[16] Furthermore, an alternative option to come to a shorter MRI protocol would be to assess bone marrow edema on post-contrast series, an option we recently successfully explored.[7]

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A strength of our study is that we included patients at early disease stage when inflammation is usually limited and MRI may be of additional value in detecting it. Furthermore, we did not limit inclusion to a single diagnosis, which makes our results more widely applicable.

A limitation is that we only assessed wrist joints and not MCP joints. We chose this for time reasons, as we prioritized to acquire axial T2-weighted fat suppressed images in order to have optimal sequences for assessment of synovitis and especially tenosynovitis without contrast administration. Secondly, we only made cross-sectional comparisons, so the sensitivity to change, which is important for clinical trials, could not be assessed. However, as cross-sectional data alone documented that non-contrast enhanced sequences cannot replace contrast-enhanced sequences, longitudinal data are less relevant. Thirdly, we used the RAMRIS method, which has only been validated in RA. However, no method exists that has been validated across multiple rheumatologic conditions and the RAMRIS is the best available validated method to assess synovitis, thus we considered it appropriate to use the RAMRIS method. Likewise, we also used the best available method to assess tenosynovitis. Finally, our data were obtained in early arthritis patients with relatively low inflammation scores, and may not be generalizable to patients with more advanced disease.

In conclusion, eliminating Gd contrast results in low specificity for synovitis and low sensitivity for tenosynovitis. Consequently, MRI without Gd contrast administration cannot be recommended for evaluation of synovitis and tenosynovitis in early arthritis patients.

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