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Aiming for a shorter scanning protocol in early arthritis MRI: can gadolinium contrast administration be eliminated?

W. Stomp, A. Krabben, D. van der Heijde, T. W. J. Huizinga, J. L. Bloem, M. Østergaard, A. H. M. van der Helm-van Mil, M. Reijnierse

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ABSTRACT

Objective

Magnetic Resonance Imaging (MRI) is increasingly used in Rheumatoid Arthritis (RA) research to depict local inflammation. According to the RAMRIS-protocol intravenous (IV) contrast is administered to assess synovitis and tenosynovitis. We studied whether IV-contrast can be eliminated, decreasing imaging time, cost and invasiveness.

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 RAMRIS, and for tenosynovitis in ten compartments. Scores of MR-images without IV-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 contrast was 91% and 72%, respectively, for the two readers and specificity 51% and 81%, with contrast-enhanced images as reference standard. 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 IV-contrast decreased specificity for synovitis and sensitivity for tenosynovitis, indicating that IV-contrast remains essential for an optimal assessment.

INTRODUCTION

Magnetic Resonance Imaging (MRI) is increasingly used in research of Rheumatoid Arthritis (RA). MRI has high sensitivity to depict local inflammation in the form of synovitis, tenosynovitis and bone marrow edema.[1] The scanning protocol is standardized in the OMERACT Rheumatoid Arthritis MRI scoring (RAMRIS) method.[2] OMERACT recommended MRI sequences include non-contrast enhanced T2 weighted fat saturated images (T2) or short tau inversion recovery (STIR) images to evaluate bone marrow edema,[2] whereas pre- and post-gadolinium contrast T1-weighted images (T1Gd) have been recommended for evaluation of synovitis and tenosynovitis.[2–4]

The use of intravenous (IV) gadolinium contrast has drawbacks; it is an invasive procedure, it is costly and it prolongs the imaging required time. Synovitis and tenosynovitis normally exhibit high signal intensity both on T2 and T1Gd images (illustrated in Supplementary Figure 1). We therefore hypothesized that it is possible to evaluate synovitis and tenosynovitis on T2 instead of T1Gd. When IV-contrast administration could be eliminated this would make MRI more patient-friendly and would increase accessibility.

The objective of this study was to determine whether IV contrast administration could be eliminated from the scanning 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 above-mentioned material and two previous studies.

MATERIALS AND METHODS

Patients

Between July 2011 and April 2012 MR imaging was performed in 93 early arthritis patients at the first visit of the Leiden Early Arthritis Clinic; for further reading on the Leiden EAC see.[5] These patients were part of a larger group in whom MRI was performed; the current study concerns a subgroup 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 at the most painful or the dominant side in case of equally severe symptoms. Coronal T1-weighted images and coronal and axial T2-weighted images with fat suppression were acquired. After IV contrast injection, coronal and axial T1-weighted images with fat suppression were acquired (full MRI protocol provided in the Supplementary Methods).

Anonymized datasets were scored twice by two experienced readers (WS and AK), using all acquired images (Gdset), and using only unenhanced images (T2set). The order of examinations was randomized 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 carpometacarpophalangeal joints.[2] Tenosynovitis was evaluated in 10 tendons/compartments on a 0-3 scale as described by Haavardsholm et al.[4]

Reference standard and statistics

Gadolinium enhanced image scores were the reference standard. Comparisons were made for the two readers independently and for the agreement between readers. To determine whether the same absolute scores were obtained by both methods, scores were compared with weighted kappa statistic and intra class correlation coefficient (ICC) for absolute agreement. Furthermore, the sensitivity and specificity were calculated at both joint/tendon level and at patient level, with scores ≥1 considered positive at both joint/tendon and patient level.

Literature review and pooled data analysis

Available literature up to November 2013 was searched; central terms in our search were 'arthritis', 'synovitis', 'tenosynovitis', 'gadolinium contrast' and 'MRI' (full search strategy provided in the Supplementary Methods). Studies comparing findings on MRI for synovitis and tenosynovitis with and without IV-contrast were reviewed. For synovitis we performed a pooled data analysis; raw data were obtained from the literature[6] or obtained via personal communication[7] and combined to determine overall test characteristics. For tenosynovitis, due to different scoring systems used we could not perform a pooled data analysis.

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 Supplementary table 1. 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 1). 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 contrast. ICCs between the T2set (without contrast) and Gdset (with gadolinium 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 gadolinium 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 1).

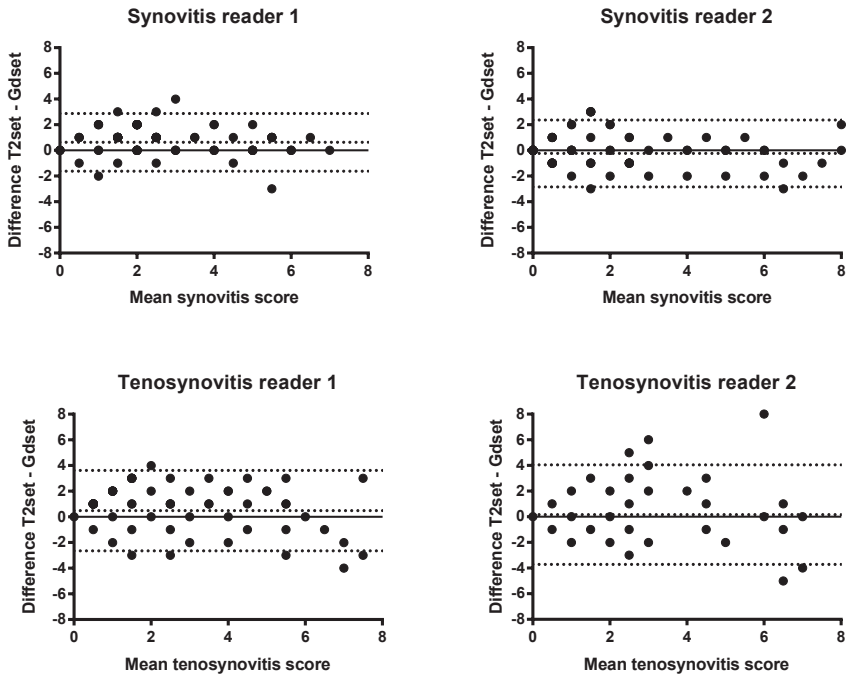

Figure 1: Bland-Altman plots of assessment of synovitis and tenosynovitis with and without gadolinium enhancement

Bland-Altman 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 en lower lines show the ± 95% limits of agreement. For tenosynovitis variation increases with higher scores for reader 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.

Table 1: 2x2-table, and sensitivity and specificity of assessment of synovitis and tenosynovitis at joint/tendon level and at patient level without contrast injection, 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) IV 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.

Test characteristics on joint/tendon level

The sensitivity to detect synovitis without gadolinium 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 1).

Large discrepancies in scores in individual joints/tendons

Differences ≥ 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. Importantly for synovitis, in all cases areas of high signal on T2 were seen without enhancement on T1Gd images, indicating false-positive results on T2 due to effusion (Fig. 2). For tenosynovitis no clear explanation was found.

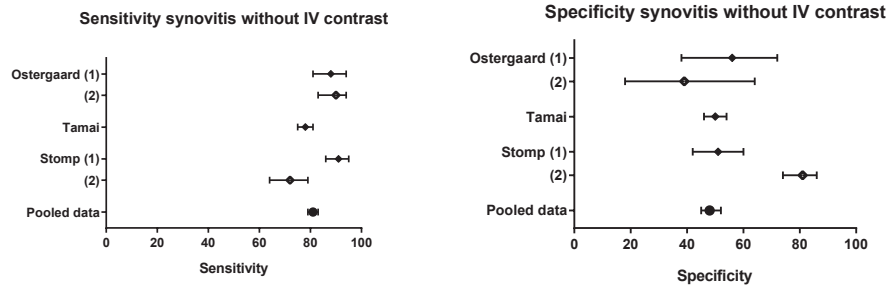

Figure 2: Sensitivity and specificity of evaluation of synovitis without IV contrast in separate studies and in a combined analysis

Plot of sensitivity and specificity estimates of MRI without IV contrast 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.

Literature review and pooled data analysis

Supplementary table 2 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.[6–8] The tendency on the findings on joint/tendon level were 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 sensitivity was low.[7] Figure 2 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

gadolinium was 81% and the overall specificity 50% (Figure 2, Supplementary table 3). For tenosynovitis no pooling could 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 IV gadolinium contrast administration 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-IV contrast sequences.

Gadolinium 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.[9] For assessment of bone marrow edema and erosions no gadolinium contrast is necessary.[6,7] However, based on our findings and the literature review, IV contrast is necessary for optimal assessment of synovitis and tenosynovitis.

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 injection. Secondly, we only made cross-sectional comparisons, so sensitivity to change, important for clinical trials, could not be compared. However, as cross-sectional data alone documented that non-contrast enhanced sequences cannot replace contrast-enhanced, longitudinal data are less relevant. 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 gadolinium contrast gave a low specificity for synovitis and low sensitivity for tenosynovitis. Consequently, MRI without IV contrast injection cannot be recommended for evaluation of synovitis and tenosynovitis.

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Supplementary table 1: Patient characteristics

	Patients (n=92)	EAC total population (1993-2011, n=2748)	P value
Age, years (mean, SD)	55.8 ±13.5	51.6±17.1	0.02
Female sex, n (%)	49 (53.3)	1640 (59.7)	0.22
Symptom duration in weeks, median (IQR)	13.0 (4.8-29.0)	14.0 (6.0-31.0)	0.67
Swollen joint count (66-SJC), median (IQR)	3.0 (2.0-5.8)	4.0 (2.0-9.0)	0.22
Tender joint count (68-TJC), median (IQR)	6.5 (2.3-10.0)	5.0 (3.0-9.0)	0.21
RF positive, n (%)	28 (30.4)	800 (29.5)	0.85
ACPA positive, n (%)	23 (25.0)	628 (28.0)	0.52
Patient classification at baseline, n (%)			
RA (2010 criteria)	35 (38.0)	1060 (38.6)	0.92[#]
Undifferentiated arthritis	36 (39.1)	827 (30.1)	
Inflammatory osteoarthritis	6 (6.5)	127 (4.6)	
Psoriatic arthritis	7 (7.6)	187 (6.8)	
Other rheumatic diagnoses	8 (8.7)	547 (19.9)	

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. A chi-square test was used for nominal variables and the Student's t test or Mann-Whitney U-test for continuous variables. Student's t test was performed when variables are presented as mean and a Mann-Whitney U-test was performed when variables are presented as median. [#]The frequency of RA versus non-RA was tested.

Supplementary table 2: Overview of literature regarding the need of gadolinium contrast for assessment of synovitis and tenosynovitis

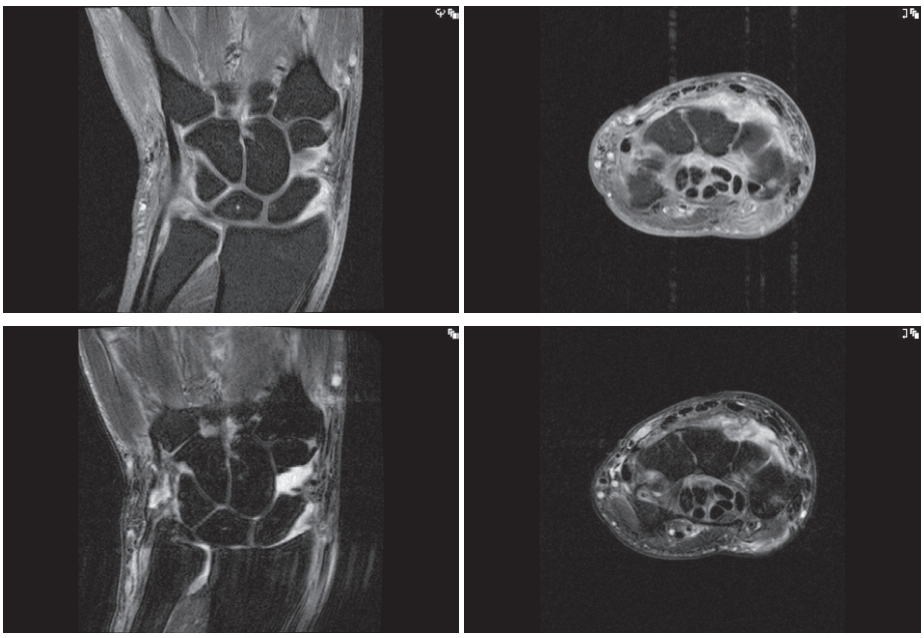
Study	*Patient group*	*MR*	*Joint area*	*Scoring method*	*Disease duration (mean/median)*	*ICC Gd+ vs Gd-*	*Sensitivity / specificity*	*Conclusion*
				Synovitis				
Ostergaard 2009	RA (n=40)	1.0/1.5T	10 wrist/ 30 mcp	RAMRIS	Unspecified	0.63-0.76	86-90% / 31-79%	Omitting IV contrast decreases reliability of synovitis scores
	RA (n=45) healthy (n=9)	0.2T Extremity	Wrist and mcp	RAMRIS	Unspecified	0.61	60% / 96%	
Tamai 2012	Early RA (n=51)	1.5T	Wrist, mcp and pip	RAMRIS	5 months	-	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 IV contrast administration; current study results also shown. Sensitivity and specificity shown are those reported for individual joints/tendons.

Supplementary table 3: Pooled data from literature for synovitis: 2x2-table, and sensitivity and specificity of assessment of synovitis and tenosynovitis at joint/tendon level without contrast injection, with contrast enhanced MRI findings as standard reference.

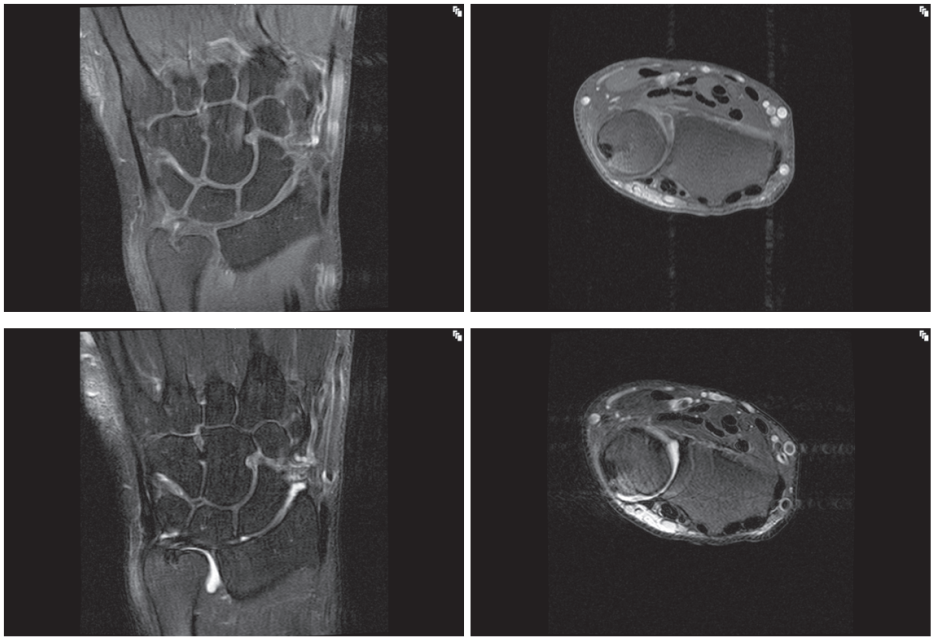
Ostergaard at el.	Gdset+	Gdset-	Total	
T2set+	101	16	117	PPV: 86%
T2set-	13	20	33	NPV: 61%
Total	114	36	150	
	Sensitivity: 89%	Specificity: 56%		
Tamai et al.	Gdset+	Gdset-	Total	
T2set+	613	316	929	PPV: 66%
T2set-	175	312	487	NPV: 64%
Total	788	628	1416	
	Sensitivity: 78%	Specificity: 50%		
Pooled data from Stomp et al, Ostergaard et al and Tamai et al.	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.(6,7) 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.



Supplementary figure 1a

Example of synovitis and tenosynovitis as visualized by T1-weighted postcontrast and T2-weighted sequences. Upper row: T1-weighted coronal (left) and axial (right) images after gadolinium administration. Bottom row: corresponding T2-weighted coronal (left) and axial (right) images before gadolinium administration. Synovitis of the radioulnar, radiocarpal and intercarpal joints and flexor tenosynovitis is clearly visible on both sequences.



Supplementary figure 1b

Example of large discrepancy in synovitis score between T1-weighted postcontrast and T2-weighted sequences. Upper row: T1-weighted coronal (left) and axial (right) images after gadolinium administration. Bottom row: corresponding T2-weighted coronal (left) and axial (right) images before gadolinium administration. Effusion in the radioulnar and radiocarpal joints results in high signal on T2-weighted images without enhancement on post-gadolinium images.

SUPPLEMENTARY METHODS

MR imaging protocol

MR imaging of wrist was performed within two weeks after inclusion, at the most painful side, or in case of completely symmetric symptoms at the dominant side. The presence of clinical arthritis at physical examination of the wrist was not a prerequisite. MR imaging was performed on a MSK-extreme 1.5T extremity MR imaging system (GE, Wisconsin, USA) using a 100mm 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 injection: 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, 300x224, ETL7).

After intravenous injection of gadolinium 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 320x192; 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.

Literature review

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"). This yielded 1035 results (November 2013). Abstracts were screened and we selected studies that reported on findings on gadolinium contrast-enhanced images compared to findings on images obtained without gadolinium 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.