

Cover Page



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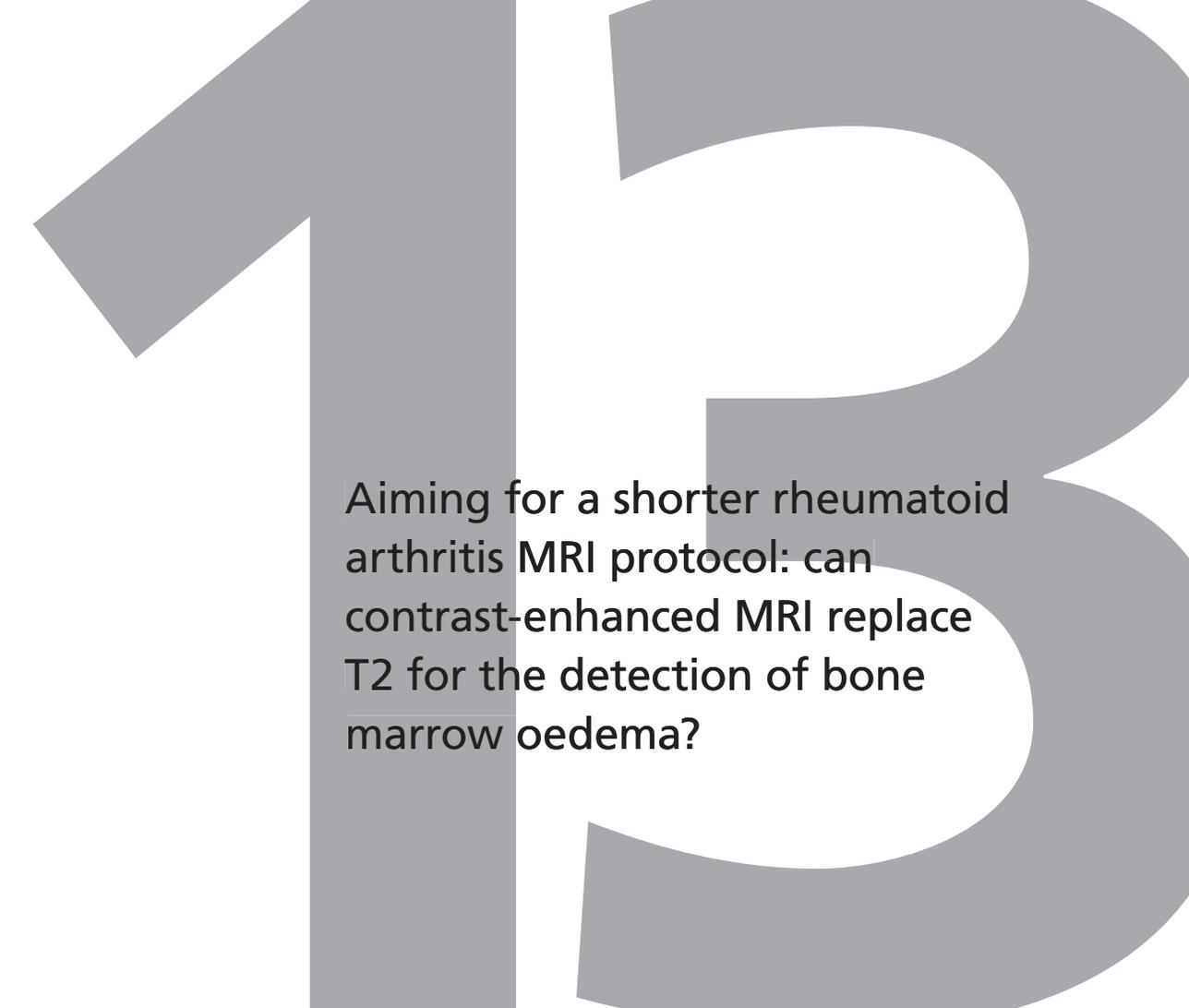
Title: Predictive factors for the development and disease course of rheumatoid arthritis

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PART 4

MRI scan protocol revisited

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Aiming for a shorter rheumatoid arthritis MRI protocol: can contrast-enhanced MRI replace T2 for the detection of bone marrow oedema?

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ABSTRACT

Objective

To determine whether T1 post-Gadolinium chelate images (T1Gd) can replace T2-weighted images (T2) for evaluating bone marrow edema (BME), thereby allowing shortening the Magnetic Resonance Imaging (MRI) protocol in rheumatoid arthritis (RA).

Methods

In 179 early arthritis patients and 43 advanced RA patients wrist and metacarpophalangeal joints were imaged on a 1.5T extremity MRI system with a standard protocol (coronal T1-, T2 fat saturated and coronal and axial T1 fat saturated after Gd). BME was scored according to OMERACT RAMRIS by two observers with and without T2-images available. Agreement was assessed using ICCs for semi-quantitative scores and test characteristics with T2 images as reference.

Results

4,048 and 989 bones were assessed in 179 early arthritis and 43 advanced RA patients respectively. Agreement between scores based on T2 and T1Gd images was excellent (intra class correlation coefficients (ICC) 0.80-0.99). On bone level sensitivity and specificity of BME on T1Gd compared to T2 were high for both patient groups and both readers (all $\geq 80\%$).

Conclusion

T1Gd and T2 images are equally suitable for evaluating BME. Because contrast is usually administered to assess (teno)synovitis, a short MRI protocol of T1 and T1Gd is sufficient in RA.

INTRODUCTION

Bone marrow edema (BME) is one of the main features of rheumatoid arthritis (RA) that can be seen on magnetic resonance imaging (MRI).^{1,2} BME is an independent predictor of subsequent radiographic progression in early RA.³⁻⁵ The OMERACT Rheumatoid Arthritis MRI Scoring system (RAMRIS) is a standardized scoring system for the assessment of synovitis, bone marrow edema and erosions on MRI in RA. It defines BME as a lesion within trabecular bone, with ill-defined margins and signal characteristics consistent with increased water content, i.e. high signal on T2-fatsat and STIR images and low signal on T1.⁶

RAMRIS recommends that imaging includes T1-weighted sequences before and following contrast agent administration, and T2-weighted images with frequency selective fat saturation (T2) or short tau inversion recovery (STIR) if frequency selective fat suppression is not available. T1-weighted images are primarily used to assess erosions and synovitis, whereas T2 images are used to evaluate BME. However, T1-weighted sequences with gadolinium-chelate (Gd) contrast-enhancement and fat-suppression (T1Gd) produce images very similar to T2 images (Figure 1). Although the RAMRIS core set of MRI acquisitions does not describe the use of fat-suppression for the post-contrast T1, in practice this is routinely used to enhance visibility of enhancement and to differentiate enhancement from fatty tissue on fast spin echo sequences, which exhibit a high signal of fat secondary to J-coupling.⁷ Previous studies performed in the knee, ankle and foot have shown that T2- fat-suppressed or STIR images and T1Gd MRI images demonstrate almost identical imaging patterns for BME.^{8,9}

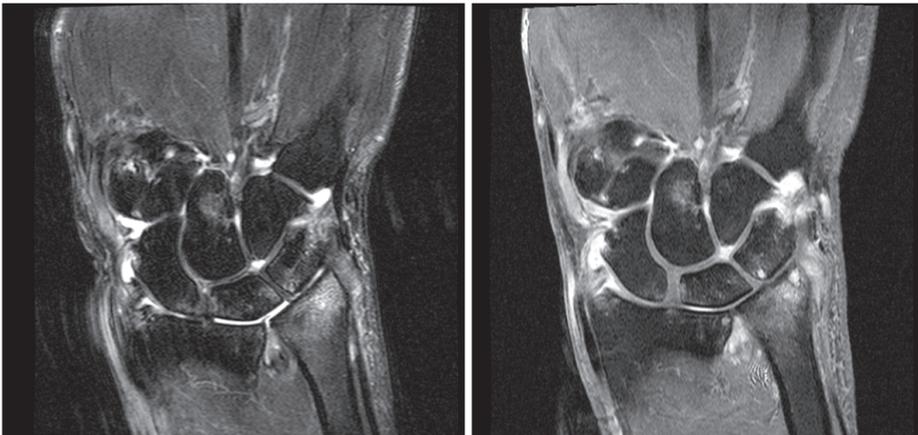


Figure 1: Typical appearance of BME on both sequences

Coronal T2 weighted fat-suppressed (a) and contrast enhanced T1-weighted fat-suppressed images (b) of the wrist in the same patient showing an almost identical pattern of BME. The majority of high intra-articular signal on T2 (a) enhances (b) consistent with synovitis; a small amount of fluid is present in the radiocarpal joint.

Scanning of unilateral hand, wrist and foot joints according to RAMRIS protocol takes >60 minutes. T1Gd images form an essential part of the protocol as they are essential to assess synovitis and tenosynovitis.¹⁰⁻¹² If T1Gd images could also be used to score BME in small hand and foot joints, valuable imaging time might be saved by leaving out T2 sequences which account for approximately 20-25% of the examination time. A shorter protocol would reduce costs and the discomfort of patients and increase the accessibility of MR. Therefore we aimed to evaluate whether T1Gd images can replace T2 images for scoring of BME, without loss of information. We studied patients with early arthritis and active advanced RA to ensure that the results observed were not dependent on the severity of the BME lesions.

MATERIALS AND METHODS

Patients

Two groups of patients were studied. The first group consisted of 179 patients presenting with early arthritis to the rheumatologic outpatient clinic of the Leiden University Medical Center, the Netherlands. Forty-three (24%) of these patients fulfilled the ACR87 criteria for RA, the others were diagnosed as undifferentiated arthritis (n=88, 49%), inflammatory osteoarthritis (n=12, 7%), psoriatic arthritis (n=15, 8%) and other rheumatic diagnoses (n=21, 12%). The median age was 57 years (interquartile range (IQR) 45-66) and 99 (55%) were female. Forty-five (25%) patients were anti-citrullinated peptide antibody (ACPA) positive. The median disease activity score (DAS44) score was 2.5 (IQR 1.9-3.0).¹³

The second group consisted of 43 advanced RA patients with RA according to ACR87 criteria with a DAS44 higher than 2.4. Their disease was active despite treatment with conventional disease modifying anti-rheumatic drugs including maximal tolerable doses of methotrexate. The median age was 57 (IQR 51-62) and 31 (72%) were female. All advanced RA patients were positive for ACPA.

MRI

Examinations were performed on a MSK Extreme 1.5 Tesla extremity scanner (GE, Wisconsin, USA). The complete recommended RAMRIS imaging set was acquired for the wrist and MCP. Joints were scanned at the most painful, or if indifferent, dominant side.

The following sequences were acquired: T1-weighted fast spin echo (FSE) sequence in the coronal plane (repetition time (TR)/echo time (TE) 650/17 ms; acquisition matrix 388 × 288; echo train length (ETL) 2); T2-weighted FSE sequence with frequency selective fat saturation in the coronal plane (TR/TE 3000/61.8 ms; acquisition matrix, 300 × 224, ETL 7). All sequences were acquired separately for the wrist and MCP joints, limited by the field of view of 100mm. Gd-chelate contrast agent (gadoteric acid, Guerbet, Paris, France)

was administered intravenously at a standard dose of 0.1 mmol/kg. After injection, T1-weighted FSE sequence with frequency selective fat saturation (T1Gd) in the coronal plane was performed (TR/TE 650/17 ms, acquisition matrix 364 × 224, ETL 2) and a T1Gd in the axial plane (TR/TE 570/7 ms; acquisition matrix 320 × 192; ETL 2). Again all sequences were acquired for both wrist and MCP joints. Field-of-view was 100mm for all sequences. Coronal sequences had 18 slices with a slice thickness of 2mm and a slice gap of 0.2mm while the axial sequence had 20 slices with a slice thickness of 3mm and a slice gap of 0.3mm.

Image assessment

BME was defined as a lesion within the trabecular bone with ill-defined margins and high signal intensity on the T2 or T1Gd images. It was scored on a 0-3 scale for each bone according to OMERACT RAMRIS score by two trained readers independently.⁶ Scores were defined as 0=0%; 1=1-33%; 2=34-66%, 3=67-100% of bone affected up to 1 cm from the joint. In case of erosions or cysts, this percentage corresponds to the part of the remaining bone affected. Scoring was performed once on T2 images and a second time on T1Gd at least two weeks apart and with images anonymized and their order randomized between sessions. 14% of the early arthritis MRI imaging sets were read twice to determine the intra-reader reliability of scoring.

Image quality was assessed by one reader separately for the T2 weighted and T1Gd images on a 0-4 scale. Scores assigned were 0 completely not assessable, 1 partly not assessable, 2 poor, 3 adequate and 4 good image quality, taking into account motion artifacts, signal and contrast to noise ratios and other factors influencing image quality.

Statistics

Image quality scores were compared by Wilcoxon signed ranks test. Differences in BME scores were compared using a paired Student's t-test and the correlation between the sequences was assessed using a Pearson correlation coefficient. Because it is desirable for scores on both sequences to have not only good correlation, but also to yield similarity in absolute BME scores, agreement between scores was assessed using intra class correlation coefficients (ICC) for absolute agreement. Agreement was also visualized by means of Bland-Altman plots in order to detect systemic biases.

Assessments for the presence or absence of BME were made both on individual bone level and at patient level (BME present in any joint). At bone level, a score of ≥ 1 in any individual bone was considered positive. Similarly, at patient level, a total score of ≥ 1 was considered positive. Sensitivity and specificity of T1Gd were determined with presence of BME on T2 as the reference standard. When values were missing on either T1Gd or T2, these bones were discarded from both assessments. The data of both readers were assessed separately, to validate that results obtained were not based on one single reader. We decided that, in

order to be able to replace T2 with T1Gd, acceptable levels of agreement were: Pearson correlation coefficient and ICC of ≥ 0.80 and sensitivity $\geq 80\%$ as assessed by two readers.

RESULTS

In the early arthritis group three patients did not receive Gd due to the presence of a low estimated glomerular filtration rate or refusal of the patient. Thus in 176 early arthritis and 43 advanced RA patients, 4048 and 989 bones were evaluated. The intra-reader ICCs for BME on T2 were 0.96 for reader 1 and 0.72 for reader 2. Missing values were present for reader 1 and 2 in 22 and 39 (0.5-1.0%) bones on T2 and 20 and 21 (0.5-0.5%) bones on T1Gd in early arthritis and 24 and 36 (2.4-3.6%) bones on T2 and 21 and 23 (2.1-2.3%) bones on T1Gd in advanced RA patients.

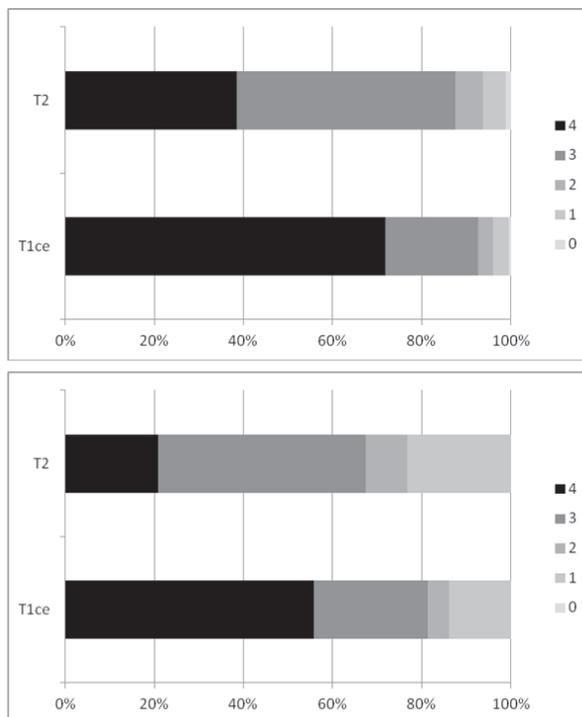


Figure 2: Image quality

Image quality for both sequences in early arthritis (a) and advanced RA (b). Scores: 4 good image quality, 3 adequate image quality, 2 poor image quality, 1 partly not assessable, 0 completely not assessable.

Image quality

In early arthritis patients, BME could be assessed in 174 patients on T2 (98.9%) and 175 patients on T1Gd (99.4%). Images were partly not assessable (image quality score 1) in nine patients on T2 and six patients on T1Gd. In advanced RA BME could be assessed in all 43 patients, although images were partly not assessable in ten patients on T2 and six patients on T1Gd. In both patient groups incomplete fat suppression was the reason for being partly not assessable. Completely not assessable scans were very rare (less than 2%, see Figure 2) and were all caused by excessive motion artifacts. Overall image quality was rated better on T1Gd than on T2 images. The median image quality score was four on T1Gd and three on T2 in both early arthritis and advanced RA (both $p < 0.001$). In case of partly not assessable images (score of 1), the parts of the image that were assessable were still used for all further analyses.

Table 1. Presence and scores of BME and measures of correlation and test characteristics at patient level

	<i>Early arthritis (n=176)</i>		<i>Advanced RA (n=43)</i>	
	Reader 1	Reader 2	Reader 1	Reader 2
	Prevalence			
BME prevalence, T2	143 (81.3%)	152 (86.4%)	41 (95.3%)	40 (93.0%)
BME prevalence, T1Gd	146 (83.0%)	159 (90.3%)	40 (93.0%)	43 (100%)
Concordance of T2 and T1Gd for presence of BME	165 (93.8%)	155 (88.1%)	40 (93.0%)	40 (93.0%)
Sensitivity of T1Gd (95% CI)	97.2% (92.5-99.1%)	95.4% (90.4-98.0%)	95.1% (82.2-99.2%)	100.0% (89.0-100%)
Specificity of T1Gd (95% CI)	78.8% (60.6-90.4%)	41.7% (22.8-63.1%)	50.0% (2.7-97.3%)	0.0% (0.0-69.0%)
	Scores			
Median score T2 (IQR)	3 (1-6)	3.5 (2-9)	8 (3-20)	6 (2-20)
Median score T1Gd (IQR)	3 (1-6)	5 (2-9)	7 (3-19)	8 (5-17)
ICC between T2 and T1Gd (95% CI)	0.99 (0.98-0.99)	0.87 (0.82-0.90)	0.99 (0.98-0.99)	0.93 (0.86-0.96)
- ICC, Wrist only (95% CI)	0.98 (0.97-0.98)	0.86 (0.81-0.90)	0.99 (0.99-1.00)	0.94 (0.88-0.96)
- ICC, Metacarpals only (95% CI)	0.98 (0.97-0.98)	0.85 (0.80-0.88)	0.90 (0.81-0.94)	0.80 (0.66-0.89)

Paired t-test was applied to test for differences in median scores between T2 and T1gd in early arthritis: $p=0.73$ (reader 1) and 0.27 (reader 2); and in advanced RA: $p=0.91$ (reader 1) and 0.52 (reader 2). Presence of BME defined as a score of ≥ 1 . T2 sequence is the reference standard for sensitivity and specificity. Intra reader ICC's for agreement between scores based on T2 and on T1Gd.

Prevalence of BME in RA

In early arthritis patients, BME (a score of ≥ 1) was present in 143 (81.3%) and 152 (86.4%) patients on T2 images and 146 (83.0%) and 159 (90.3%) patients on T1Gd images for reader 1 and 2 respectively (Table 1). In advanced RA patients, BME was present in 41 (95.3%) and 40 (93.0%) patients on T2 images and 40 (93.0%) and 43 (100.0%) patients on T1Gd images for reader 1 and 2 respectively. Thus BME was present in the majority of patients in both groups. BME scores were higher in advanced than in early RA (Table 1).

When evaluating the presence of BME in individual bones, in early arthritis BME was present in 677 (16.7%) and 921 (23.1%) bones on T2 images and 683 (17.0%) and 1023 (25.6%) bones on T1Gd for reader 1 and 2 respectively (Table 2). Likewise, in advanced RA patients, BME was present in 311 (32.7%) and 299 (31.3%) bones on T2 images and 307 (32.3%) and 372 (39.0%) bones on T1Gd images for reader 1 and 2.

Table 2. Presence of BME and test characteristics in individual bones

	<i>Early arthritis (n=176)</i>		<i>Advanced RA (n=43)</i>	
	Reader 1	Reader 2	Reader 1	Reader 2
	Individual bone level			
Total bones	4048		989	
Missing values, T2	22 (0.5%)	39 (1.0%)	36 (3.6%)	24 (2.4%)
Missing values, T1Gd	21 (0.5%)	20 (0.5%)	23 (2.3%)	21 (2.1%)
Assessed bones	4017	3995	950	955
BME prevalence, T2	677 (16.7%)	921 (23.1%)	311 (32.7%)	299 (31.3%)
BME prevalence, T1Gd	683 (17.0%)	1023 (25.6%)	307 (32.3%)	372 (39.0%)
Concordance of T2 and T1Gd for presence of BME	3839 (95.6%)	3523 (88.2%)	894 (94.1%)	814 (85.2%)
Discordance >1 point	5 (0.1%)	21 (0.5%)	21 (2.2%)	10 (1.0%)
- Sensitivity of T1Gd	87.3% (84.5-89.7%)	80.0% (77.3-82.5%)	90.4% (86.4-93.3%)	88.6% (84.3%-91.9%)
- Specificity of T1Gd	97.2% (96.6-97.8%)	90.7% (89.6-91.7%)	95.9% (94.0-97.3%)	83.7% (80.6-86.4%)

BME=bone marrow edema. Presence of BME defined as a score of ≥ 1 . T2 sequence is the reference standard for sensitivity and specificity. Intra reader ICC's for agreement between scores based on T2 and on T1Gd.

Comparison of BME evaluated on a semi-quantitative scale

First we compared the BME scores between both sequences (Table 1). In early arthritis patients, median scores were 3 on T2 and 3.5 on T1Gd for reader 1 ($p=0.73$) and 3.5 on T2 and 5 on T1Gd images for reader 2 ($p=0.27$). In advanced RA patients, median scores were 8 on T2 and 7 on T1Gd for reader 1 ($p=0.91$) and 6 on T2 and 8 on T1Gd images for reader 2 ($p=0.52$).

Figure 3 shows scores based on T1Gd plotted against scores on T2, showing a high degree of correlation between scores on T2 and T1Gd (early arthritis $r=0.99$ and 0.87 for reader 1 and 2, and advanced RA $r=0.99$ and 0.94).

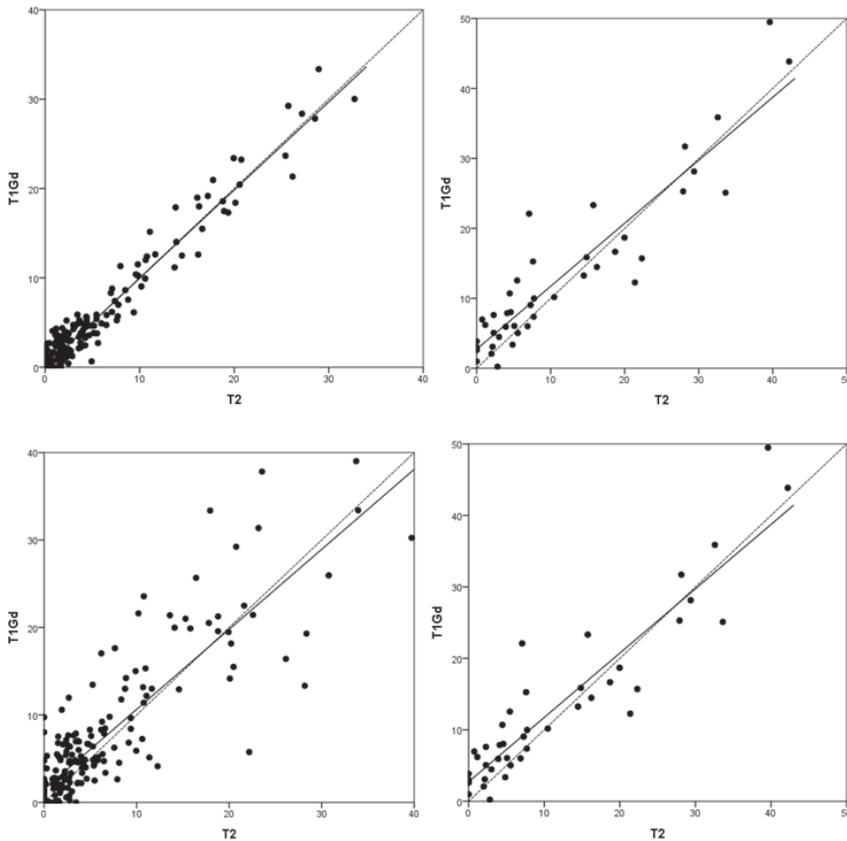


Figure 3: Correlation between total BME scores scored on T1Gd and T2 sequences.

Scores for observer 1 in early arthritis (a) and advanced RA (b) and for observer 2 in early arthritis (c) and advanced RA (d). Scores on T2 on the horizontal and scores on T1Gd on the vertical axis. Solid line: linear regression line; dashed line indicates the best possible (1:1) correlation.

Subsequently the level of agreement of scores obtained on T2 and T1gd were evaluated using ICCs. In early arthritis, the ICC's for both readers were 0.87 and 0.99; in advanced RA these were 0.99 and 0.93 (Table 1). Bland-Altman plots (Figure 4) revealed little systematic differences (reader 2 had slightly higher scores on T1Gd) and acceptable 95% limits of agreement for the differences in scores.

Comparison of the presence or absence of BME

For clinical application, determining the presence or absence of BME might be more important than the score on a semi-quantitative scale. We assessed test characteristics of T1Gd with T2-images as the reference standard with a score of ≥ 1 as cut-off for positivity. Analyses were done at the individual bone level and showed that sensitivity was $\geq 80\%$

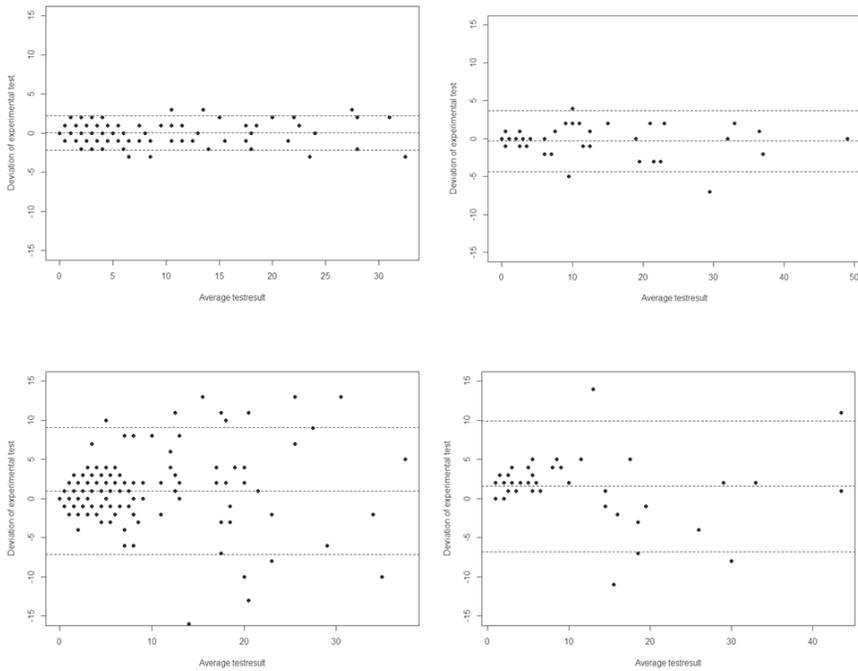


Figure 4: Bland-Altman plots of total patient BME scores on T1Gd and T2 sequences
 Bland-Altman plots for observer 1 in early arthritis (a) and advanced RA (b) and for observer 2 in early arthritis (c) and advanced RA (d). The difference (T1Gd-T2) between paired measurements are plotted against the mean of the two measurements. The middle line in each graph shows the bias between the two measurement methods. The observation that the line is located around 0 indicates that systematic bias was low; although reader 2 achieved slightly higher scores on T1Gd and showed some heteroscedasticity on both sequences (variance increases with an increase in score), which was also present to a lesser extent in advanced RA for reader 1. The dashed lines show the \pm 95% limits of agreement.

and specificity $\geq 83\%$ (Table 2) in the various tested combinations. When evaluating the test characteristics of the presence of BME at the patient level, also a high sensitivity was observed, $\geq 95\%$ for both readers. However, the specificity was low with a broad 95%CI, which is partly explained by the low number of patients without BME (17-33 early arthritis patients and 0-3 advanced RA patients depending on reader and sequence). A high level of agreement between T1Gd and T2 was also illustrated by the high concordance in bones that were scored as having BME and the low frequency of discordance of more than one point ($\leq 0.5\%$ in early RA and $\leq 2.2\%$ in advanced RA (Table 2).

Reliability analysis (inter-reader agreement)

Finally we also assessed the reliability of scoring between both readers when evaluating T2 or T1Gd. The ICCs were high for both sequences (all ≥ 0.83 , Table 3), indicating good inter-reader agreement under all investigated conditions.

Table 3. Interreader ICCs for BME scores at patient and bone level

	<i>Patient</i>		<i>Bone</i>	
	<i>Early arthritis</i>	<i>Advanced RA</i>	<i>Early arthritis</i>	<i>Advanced RA</i>
T2 BME	0.86 (0.80-0.90)	0.91 (0.84-0.95)	0.77 (0.75-0.79)	0.86 (0.84-0.88)
- Wrist	0.90 (0.86-0.93)	0.96 (0.92-0.98)	0.79 (0.77-0.80)	0.87 (0.85-0.89)
- Metacarpals	0.75 (0.67-0.81)	0.67 (0.45-0.81)	0.71 (0.68-0.74)	0.81 (0.75-0.86)
T1Gd BME	0.88 (0.69-0.94)	0.93 (0.87-0.96)	0.80 (0.77-0.82)	0.85 (0.83-0.86)
- Wrist	0.89 (0.72-0.95)	0.95 (0.90-0.97)	0.80 (0.76-0.83)	0.84 (0.82-0.87)
- Metacarpals	0.83 (0.77-0.88)	0.66 (0.46-0.80)	0.78 (0.75-0.80)	0.85 (0.81-0.87)

Inter reader ICCs for total BME score per patient and for individual bone scores between the two readers, by patient group and imaging sequence used.

DISCUSSION

T1Gd images have almost the same yield as T2 images in displaying BME. Our results show that BME is equally well assessed on either sequence. Thus, when coronal fat-suppressed T1 weighted images after Gd-chelate contrast administration are routinely obtained as part of the imaging protocol, as is the case within the OMERACT RAMRIS core imaging set, T2 or STIR images are redundant and can be eliminated from the imaging protocol, reducing total imaging time by approximately 20-25%.

Historically RA has been considered a disease that mainly involved the synovium, with erosions caused by pannus invasion. It was only after the introduction of MRI that it was observed that inflammatory processes take place within the bone, as reflected by BME-like abnormalities on MR. Although for some years it remained unclear what the significance of BME was, it has now been shown that BME detected by MRI reflects the formation of inflammatory infiltrates in the bone marrow in RA.¹⁴ Histological examination of BME reveals a number of cell types, including macrophages, plasma cells, CD8+ T cells and B cells.¹⁵ Stressing the importance of this process is the finding that BME is the strongest imaging predictor of erosive progression that has been identified to date.¹

On MRI BME can be observed due to the focally increased water content in the bone marrow, partly or entirely replacing normal bone marrow fat. Signal intensity is low on T1 sequences and high on T2 or STIR sequences. BME also enhances with intravenous Gd.¹⁶ The appearance of bone marrow on T1Gd images is very similar to T2 or STIR images before Gd contrast administration.^{8,9}

Previously it has been shown in the knee, ankle and foot of patients with non-rheumatic diseases that T2 or STIR images and T1Gd images are equally suitable to assess BME and other bone marrow abnormalities.^{8,9} In early RA, findings from Tamai et al. suggest that T1Gd images visualize bone marrow edema with high specificity compared to T2.¹¹ Our

study is, as far as we know, the first focussing specifically on the sequences required to image BME in RA.

The standardized use of fat suppression on the T1Gd sequence aids in identifying enhancing BME in the fatty bone marrow. Protons in both fatty and aqueous environment have high signal intensity on T2FSE and can be differentiated by using fat saturation, identifying the water as high signal intensity (Figure 1a). Nowadays fat saturation in combination with T2FSE is routinely included in musculoskeletal imaging protocols. The same additional value of fat saturation is used in the contrast enhanced T1FSE sequences, facilitating the depicting of Gd enhancement (high on T1) in the high signal intensity of fatty marrow (Figure 1b). Our results show that detection of BME on T1Gd is similar to that on T2 images. In addition, better image quality favors the T1Gd sequence. One limitation of using only T1Gd sequence is that small effusions, bright on T2 but not enhancing on T1Gd, may be harder to detect. Three patients did not receive Gd and thus these could be considered failures for the T1Gd images; however whenever contrast administration is not feasible, T2 can always be used as a fallback option.

Within the imaging protocol for arthritis as used in our hospital, the T2 sequence takes approximately four minutes out of twenty for the complete protocol for one joint area. Thus eliminating the T2 sequence from the imaging protocol results in a 20% reduction of imaging time. Especially when imaging multiple joint areas in one session, shortening of the imaging time in combination with more robust sequences decreases the chance of unsuccessful MRI examinations.

A limitation of our study was that we performed semi-quantitative measurements rather than quantitative measurements of BME volume. However this reflects current research practice where RAMRIS is the predominantly used method of semi-quantification. Moreover, previous studies have shown the measured volume of BME to be almost identical regardless of imaging sequence.^{8,9} Also, our method requires the administration of Gd, however this is usually not an issue, as this is needed for the assessment of synovitis and tenosynovitis.

Strengths of our study include the large number of patients studied, the inclusion of both early arthritis and advanced rheumatoid arthritis patients and the data having evaluated by two readers. The consistency in the findings between readers and between patients with different severity of BME lesions and different severity of RA support the validity of our results.

In conclusion, T1Gd and T2 images are equally suitable for scoring BME in early arthritis patients and advanced RA. For RAMRIS scoring, a short protocol of T1 and T1Gd is sufficient.

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