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FULL PAPER

Assessment of bone marrow oedema-like lesions using MRI in patellofemoral knee osteoarthritis: comparison of different MRI pulse sequences

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Objective: To compare bone marrow oedema-like lesion (BML) volume in subjects with symptomatic patellofemoral (PF) knee osteoarthritis (OA) using four different MRI sequences and to determine reliability of BML volume assessment using these sequences and their correlation with pain.

Methods: 76 males and females (mean age 55.8 years) with symptomatic patellofemoral knee OA had 1.5 T MRI scans. PD fat suppressed (FS), STIR, contrast-enhanced (CE) T_1W FS, and 3D T_1W fast field echo (FFE) sequences were obtained. All sequences were assessed by one reader, including repeat assessment of 15 knees using manual segmentation and the measurements were compared. We used random-effects panel linear regression to look for differences in the log-transformed BML volume (due to positive skew in the BML volume distribution) between sequences and to determine associations between BML volumes and knee pain.

Results: 58 subjects had PF BMLs present on at least one sequence. Median BML volume measured using T_1W FFE sequence was significantly smaller (224.7 mm^3, interquartile range [IQR] 82.50–607.95) than the other three sequences. BML volume was greatest on the CE sequence (1129.8 mm^3, IQR 467.28–3166.02). Compared to CE sequence, BML volumes were slightly lower when assessed using PDFS (proportional difference = 0.79; 95% confidence interval [CI] 0.62, 1.01) and STIR sequences (proportional difference = 0.85; 95% CI 0.67, 1.08). There were strong correlations between BML volume on PDFS, STIR, and CE T_1W FS sequences (ρs = 0.98). Correlations were lower between these three sequences and T_1W FFE (ρs = 0.80–0.81). Intraclass correlation coefficients were excellent for proton density fat-suppressed, short-tau inversion recovery, and CE T_1W FS sequences (0.991–0.995), while the ICC for T_1W FFE was good at 0.88. We found no significant association between BML volumes assessed using any of the sequences and knee pain.

Conclusion: T_1W FFE sequences were less reliable and measured considerably smaller BML volume compared to other sequences. BML volume was larger when assessed using the contrast enhanced T_1W FS though not statistically significantly different from BMLs when assessed using PDFS and STIR sequences.

Advances in knowledge: This is the first study to assess BMLs by four different MRI pulse sequences on the same data set, including different fluid sensitive sequences and gradient echo type sequence.

INTRODUCTION

Magnetic resonance imaging (MRI) has been widely used in knee osteoarthritis (OA) research as it permits the evaluation of abnormal changes in the joint associated with disease, including subchondral bone marrow lesions (BMLs). BMLs are common in symptomatic knee OA and are considered to be an important imaging marker which has been associated with pain[1,2] and progression of disease.[3–6] Their appearance, however, is influenced by the MRI imaging technique/sequence used. A number of MRI pulse sequences have been used to assess BMLs in clinical and research studies, including: (i) fluid sensitive sequences (T_2 weighted, proton density (PD)-weighted, intermediate-weighted sequences with fat suppression),[7–10] and short-tau inversion recovery (STIR) sequences,[8,11,12] (ii) contrast-enhanced T_1 weighted MRI sequences with fat suppression,[11–15] and (iii) gradient-echo (GRE) sequences such as dual-echo steady-state (DESS), fast low-angle shot (FLASH), or spoiled-gradient recalled acquisition in steady-state (SPGR).[16,17] There are, however, relatively few data comparing these sequences and those published have looked at BML volume assessed typically using a contrast-enhanced (CE) *vs* non-CE pulse sequence.[11–13,15] Further, most studies looked at BML volume on a relatively small number of OA patients or a heterogeneous patient population and used two or three different MRI pulse sequences only. Using data collected as part of a trial of brace therapy in patients with symptomatic patellofemoral OA, we assessed BML volume in the patellofemoral joint using four different pulse sequences including three different fluid sensitive MRI pulse sequences and a fat-suppressed GRE sequence. Our aims were: (i) to determine the reliability of BML volume assessment for each of the sequences, (ii) to compare the proportion of subjects identified with BML, and size of the BMLs, (iii) to determine between sequence correlations in BML volume, and (iv) to determine for each sequence the association between BML volume and knee pain.

METHODS AND MATERIALS

Subjects

This study was a secondary analysis of a completed randomised clinical trial of a patellar brace in participants with painful patellofemoral knee OA (Trial registration number: ISRCTN50380458).[14] The clinical trial was carried out from August 2009 to September 2012. Participants were clinically assessed by an experienced physiotherapist for knee pain on some nominated aggravating activities, such as stair climbing, kneeling, prolonged sitting or squatting[14] and those with pain score of 4 or above on 0–10 cm visual analogue scale (VAS) were enrolled in this trial.

MRI pulse sequences parameters

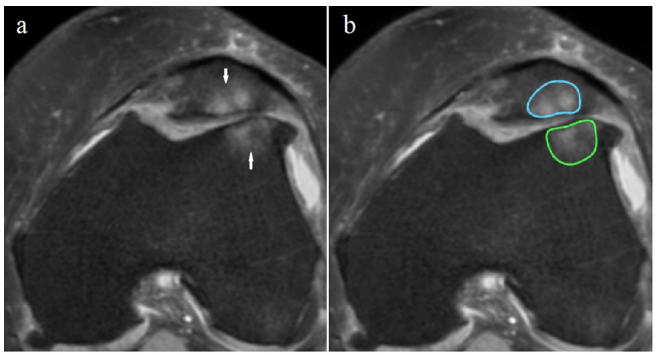
MR images were obtained on a Philips 1.5 T Scanner (Philips, Best Netherlands) using an eight channel knee coil (SENSE-Knee 8). Images of the patellofemoral joint were obtained in the axial plane using the following MRI sequences: (1) fat suppressed fast spin-echo (FSE) (TR/TE, 1500/15 ms; field of view (FOV), 14 cm; 256 × 256 pixels and 24 slices; slice thickness, 3 mm with 0.3 mm gap), referred as proton density fat-suppressed (PDFS) hereafter; (2) Short tau inversion recovery (TR/TE,~3700/14 ms; TI, 140 ms; FOV 14 cm; 320 × 320 pixels and 24 slices; slice thickness, 3 mm with 0.3 mm gap), referred to as STIR; (3) Fat suppressed post intravenous contrast agent (TR/TE, 500/17 ms; FOV 14 cm; 320 × 320 pixels and 24 slices; slice thickness, 3 mm with 0.3 mm gap) referred to as contrast enhanced T_1 weighted sequence with fat suppression or CE T_1W FS; and (4) 3D T_1 weighted GRE pulse sequence with fat suppression (TR/TE, 39/~5.2 ms; flip angle, 45°; FOV, 14 cm; 256 × 256 pixels and 53 sections; slice thickness, 3.0 mm; and overlap between adjacent slices, 1.5 mm) referred to as 3D gradient echo T_1 weighted fast field echo sequence (T_1W FFE). There were small parameter differences in two participants with some changes to the FOV (increased to 15 cm) and matrix size.

BML assessment

BML assessment was performed by a trained reader (HN) who was blinded to the pain score. Images acquired using different sequences in the same participant were not evaluated together. BMLs are defined as ill-defined high signal intensity areas adjacent to articular cartilage or cartilage loss on two or more contiguous slices. We used manual segmentation to calculate BMLs volume and focused on BMLs in the patella and trochlea of the femur (patellofemoral joint). The patella and the opposing region of the anterior femur (trochlea) were defined using regions derived from Boston-Leeds Osteoarthritis Knee Score (BLOKS), the inferior margin of the femur was the intersection between a line drawn parallel to the anterior aspect of the proximal tibia and the femoral surface[18] on sagittal 3D water-selective cartilage scans (WATSc).

Patellofemoral (PF) BMLs were delineated on each MRI slice in Osirix software, and total PF BMLs volume integrated over all slices. In the case of multifocal BMLs, the segmentation was performed for all BMLs and the total PF BML volume (in mm^3) was calculated by adding the volume of all PF BMLs in a knee. Figure 1 shows an example of the manual segmentation of multifocal BMLs. Cystic changes within BMLs were included in the BMLs volume measurements. However, simple cysts without associated oedema-like features, solitary cysts, ganglion cysts or high signal intensity within osteophytes were not included in the analysis.

Figure 1. Manual segmentation of BMLs. Axial PDFS image (a) shows BMLs in the patella and trochlea (white arrows) with area of interests were drawn for volume measurement (b). BML, bone marrow lesion; PDFS, proton density fat-suppressed.



Intrareader reliability for manual segmentation of BML volume was investigated by the reader repeating assessment of 15 knees of 4 different MRI sequences with a minimum of 4 weeks between assessments. The reader was not aware which images were repeats.

Statistical analyses

The intraclass correlation coefficient (ICC [3,1 model])[19] was used to determine intrareader reliability in BML volume for each sequence separately. ICC values range from 0 to 1, where <0.5 indicates poor reliability, 0.5 to <0.75 moderate, 0.75–0.9 good, and >0.9 excellent reliability.[20] The statistical analyses were limited to those 58 patients who had a BML on at least one of the sequences. PF BML volumes were assessed using each of the four different pulse sequences. We used a random-effects panel linear regression model to look for differences in BML volume assessed using these different sequences. Post-hoc pairwise comparisons were undertaken using Bonferroni-corrected 95% confidence intervals.[21] As the distribution of the BML volume was positively skewed, the BML volumes were first log-transformed, the model run on these transformed volumes, and the subsequent regression coeffients back-transformed to give coefficients in terms of proportions, and predicted back in mm^3. Bivariate analysis was performed using χ^2 and Wilcoxon rank sum test to compare subject characteristics between those with BMLs on all sequences and with BMLs on some but not all sequences. The association in BML volume between pulse sequences was determined using Spearman's correlation coefficient (ρs).[22] We used linear regression to evaluate the association between log BML volume on different MRI pulse sequences and VAS pain scores. A type-I error rate of 0.05 was used to assess statistical significance. All statistical analyses were performed using Stata 14.0 (StataCorp, TX, USA).

RESULTS

Subjects

There were 76 subjects (36 male, 40 female) with 4 suitable MRI pulse sequences that fulfilled the inclusion criteria. Subjects ranged in age from 41 to 70 years (mean 55.8 years; SD 7.4) and BMI 30.4 (SD 5.0) kg/m^2. Mean visual analogue scale (0–10 cm) pain score at baseline was 6.2 (SD 2.2) cm.

Table 1. Intrareader reliability for manual segmentation of BMLs (n = 15)

MRI pulse sequences	ICC values (95% confidence interval)
PDFS	0.994 (0.981 to 0.998)
STIR	0.995 (0.981 to 0.999)
CE T_1W FS	0.991 (0.973 to 0.997)
T_1W FFE	0.88 (0.582 to 0.962)

T1-w FFE, T_1 weighted fast-field echo; CE T1-w FS, contrast enhanced T_1 weighted fat-suppressed;ICC, Intraclass correlation coefficient; PDFS, proton density fat-suppressed; STIR, short tau inversion recovery.

Intrareader reliability of BML volume

Table 1 shows the $ICC_{3,1}$ for BML volume in 15 knees for the four sequences. The ICCs were excellent for PDFS, STIR and CE T_1W FS sequences (all 0.99), while the ICC for T_1W FFE was lower at 0.88.

Detection of BMLs and comparison of BML volume between different MRI pulse sequences

Among the 76 subjects with complete data, 58 had PF BMLs present on at least one sequence. BMLs were present in all 58 patients when assessed using PDFS, STIR and CE T_1W FS sequences; the T_1W FFE sequence did not demonstrate BMLs in 4 patients.

Compared to the 54 patients where BMLs were present in all sequences, those in whom a BML was not seen on the T_1W FFE sequence were of similar median age (60.5 *vs* 55.0 yrs), body mass index (28.9 *vs* 30.4 Kg/m^2), and pain score (5.9 *vs* 6.3). The volume of BMLs, assessed using the other three sequences, was smaller for these subjects. For example, using the PDFS sequence median BML volume was 206.9 mm^3 for 4 subjects without BML (on T_1W FFE) compared to a median BML volume of 1117.9 mm^3 for the other 54 subjects.

Examples of BMLs using the four MRI sequences are shown in Figure 2.

The median PF BML volume was greatest using the CE T_1W FS sequence, and smallest using the T_1Ww FFE sequence (Table 2 and Figure 3).

Post-hoc pairwise comparisons following the random-effects panel linear regression established that BML volume was similar when assessed using the PDFS, STIR, or CE T_1W FS sequences (Table 3). BML volumes assessed on T_1W FFE sequence were, on average, between 4 and 6 times lower those from any of the other three pulse sequences.

Correlation between different MRI pulse sequences

The Spearman's correlation coefficients (ρs)[22] of BML volume between sequences was very strong when assessed using PDFS, STIR, and CE T_1W FS (all ρs = 0.98). The correlation was strong between these sequences and T_1W FFE (ρs ranging from 0.80 to 0.81) (Table 4).

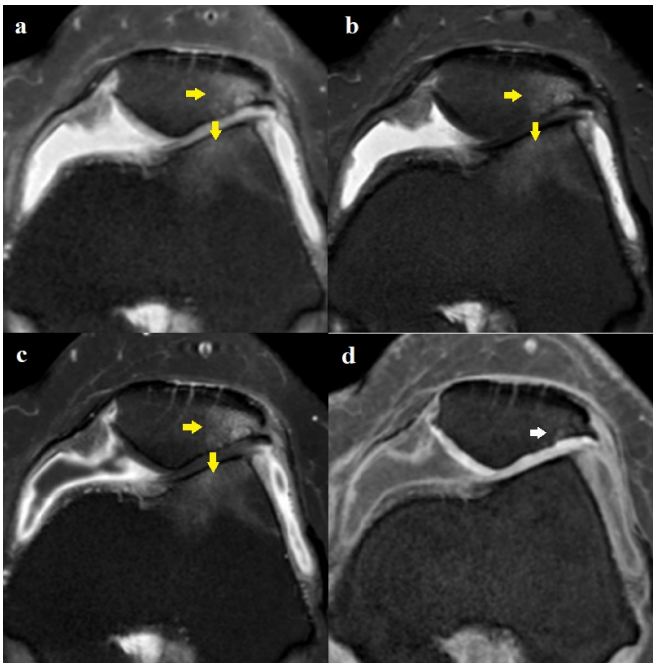
Association between MRI pulse sequences and pain

In a linear regression featuring severity of knee pain (measured on a 10 cm VAS for a patient-nominated aggravating activity) as the outcome and the log-tranformed baseline PF BML volume as a predictor for each of the four sequences, no association was found for any of the MRI pulse sequences (Table 5). The amount of pain variance explained by PF BML volumes was low for all sequences.

DISCUSSION

In this study, intrareader reliability for BML volume measurement was excellent when assessed using PDFS, STIR and CE T_1W FS ($ICC_{3,1}$= 0.991–0.995) and good for assessment using

Figure 2. Axial PDFS sequence (a) shows BMLs in the patella and femoral trochlea of the knee (yellow arrows). A similar appearance was also visible on STIR (b) and CE T_1W FS (c). However, T_1W FFE sequence (d) of the same knee shows only BML in the patella (white arrow) with no BML clearly visible in the femur. BML, bone marrow lesion; FFE, fast field echo; FS, fat-suppressed; PDFS, proton density fat-suppressed; STIR, short tau inversion recovery.



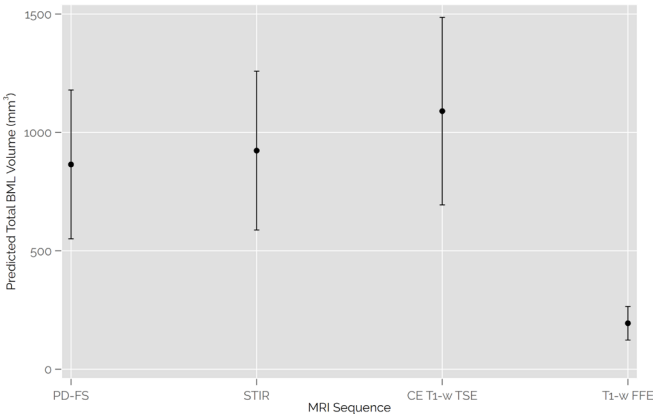
the T_1W-FFE sequence ($ICC_{3,1}$= 0.88). Approximately three quarters of subjects (58 of 76) had evidence of PF BMLs that were present on PDFS, STIR and CE T_1W FS sequences. BMLs were not seen in four of these subjects when assessed using the T_1W FFE sequence. We found that BML volume was larger using the contrast enhanced sequence though was not statistically significantly different from BMLs assessed using the PDFS or STIR sequences after Bonferroni correction. On T_1W FFE images, the BML volume was significantly smaller than the other three sequences. Significant correlations were observed between BMLs measured with all sequences. Correlations between PDFS, STIR and CE T_1W FS were very strong (ρ*s* = 0.98); correlations

Table 2. Summary of PF BML volumes (mm^3) on different MRI pulse sequences

MRI pulse sequences	Number of patients	Median BML volume (IQR)
PDFS	58	960.30 (316.47; 2705.34)
STIR	58	1056.33 (369.60; 2645.61)
CE T_1W FS	58	1129.76 (467.28; 3166.02)
T_1W FFE	58	224.70 (82.50; 607.95)

IQR, interquartile range;PDFS, proton density fat-suppressed; PF, patellofemoral;STIR, short tau inversion recovery.

Figure 3. Comparison of BML volumes between MRI pulse sequences, taken from the panel linear regression model, after back-tranformation onto the mm^3 scale. BML, bone marrow lesion; FFE, fast field echo; FS, fat-suppressed; PDFS, proton density fat-suppressed; STIR, short tau inversion recovery.



between T_1W FFE and the other sequences were lower (ρ*s* ~ 0.80).

Several studies have compared BML volume in subjects with knee OA assessed using different MRI sequences, although to our knowledge there are no studies which have looked at BML volume using both STIR and PDFS sequences. Most have compared contrast enhanced sequences with one or two other sequences.[11–13,15] Roemer et al[13] in a study of 32 patients with knee OA reported that BMLs assessed using PD-w FS were larger (38%) than when assessed using T1-w FS CE sequences, though as in our study there was a strong correlation between them. Nielsen et al[15] found BML volume measured from STIR images of the tibiofemoral compartments was slightly larger (~3%) compared to T1 post-contrast sequences using manual segmentation. Other studies with relatively small proportions of OA patients have also shown small differences between STIR and contrast enhanced T_1W FS sequences.[11,12] In our study, BML

Table 3. Comparison of BMLs volume between MRI pulse sequences

Comparison between pulse sequences	Proportional difference (Exponentiated coefficient)	Bonferroni-corrected (95% Confidence Interval)
PDFS *vs* STIR	0.94	(0.74; 1.19)
PDFS *vs* CE T_1W FS	0.79	(0.62; 1.01)
PDFS *vs* T_1W FFE	4.45	(3.48; 5.70)
STIR *vs* CE T_1W FS	0.85	(0.67; 1.08)
STIR *vs* T_1W FFE	4.75	(3.71; 6.09)
CE T_1W FS *vs* T_1W FFE	5.61	(4.38; 7.19)

BML, bone marrow lesion; FFE, fast field echo; PDFS, proton density fat-suppressed; STIR, short tau inversion recovery.

Table 4. Association between BML volume assessed using different MRI sequences: Spearman's correlation coefficients (ρs)

Pulse Sequences	STIR	CE T1-w FS	T1-w FFE
PDFS	0.98[a]	0.98[a]	0.81[a]
STIR		0.98[a]	0.80[a]
CE T_1W FS			0.81[a]

BML, bone marrow lesion; FFE, fast field echo; PDFS, proton density fat-suppressed; STIR, short tau inversion recovery.
[a]*p* value <0.05.

volume was greater when assessed using CE T_1W FS compared to other sequences. There are a number of possible reasons for the apparent difference from previous studies. In our study, TR values were shorter than the study by Roemer et al[13] on both PDFS (1500 *vs* 5080 ms) and CE T_1W FS (500 *vs* 720 ms) which could potentially result in BMLs appearing relatively smaller on PDFS and larger on CE T_1W FS images. Because the edge of BMLs is inherently poorly defined, delineation is subjective and other details of the imaging sequence may also be important in determining the precise BML volume. These details include timing of scan post-contrast administration,[23] relaxivity, and dose of contrast agent,[12] efficacy of fat suppression, and signal to noise ratio.[24] This highlights the importance of using standardized protocols including both image sequence and imaging parameters when assessing BML volume in research settings. Given the greater potential for variability using CE sequences, there may be advantages to using PDFS and STIR sequences for routine assessment.

In our study, we found that T_1W-FFE sequences detected BMLs in a smaller number of people (54 *vs* 58) and that the full extent of BMLs shown on other sequences was not captured by the T_1W FFE sequences. Furthermore, the correlation between BML volume measured on T_1W FFE and other sequences was lower (~0.80) and the intrareader reliability was also lower. There is little literature on the value of these sequence for assessing BMLs in OA. DESS sequences, however, have been studied and have also shown much lower volumes than intermediate-weighted fat suppressed images (median BML volume: DESS = 191 mm^3; IW FS = 1840 mm^3), though there was a good correlation between both sequences with a Spearman's correlation coefficient of 0.83.[25] While both DESS and T_1W FFE sequences have been used to segment articular cartilage volumes, neither appears suitable for segmenting the full extent of BMLs visualized on other sequences. However, it is possible that as with DESS, T_1W FFE sequences may be valuable for discriminating cystic components.[16,26]

Table 5. Association between baseline pain score and log-tranformed PF BMLs volume assessed using different MRI sequences

MRI Sequences	Proportional change (Exponentiated coefficient) (95% CI)	R^2	ρ_S (95% CI)
PDFS	0.91 (0.62; 1.35)	0.004	−0.07 (−0.32; 0.20)
STIR	0.90 (0.59; 1.36)	0.005	−0.06 (−0.31; 0.21)
CE T_1W FS	0.95 (0.64; 1.43)	0.001	−0.03 (−0.29; 0.23)
T_1W FFE	1.30 (0.82; 2.06)	0.025	0.10 (−0.17; 0.35)

BML, bone marrow lesion; FFE, fast field echo; PDFS, proton density fat-suppressed; ρS, Spearman's Correlation Coefficient;STIR, short tau inversion recovery.

Among our subjects, we found no significant association between BMLs volume and a patient nominated VAS pain score. Further, there was no significant difference in pain scores between those with BMLs compared to the smaller number of people (n = 18) without BMLs (data not shown). The small sample size means we can not exclude Type 2 error. Also, all of those who took part in the original clinical trial had significant knee pain (≥4 cm VAS) at baseline.

There are some limitations to consider in interpreting the results of the study. The sample size was relatively small, yet we were able to show differences in BML volume across the different sequences assessed and the number of subjects studied was larger than in many previous studies.[11–13,15] Because of the standardised imaging protocol, we did not look at the influence of contrast dose or timing on BML volume and other imaging sequence parameters which may potentially have an impact on outcome and for which further studies are needed. Our study was cross-sectional and we did not look at sensitivity to change or correlation with treatment response factors which may be important in determining an optimum imaging sequence. Finally, our data relate to BMLs assessed at the patellofemoral compartment and caution is required before generalizing the findings to other sites.

In conclusion, we found that T_1W FFE sequences were less reliable and measured considerably smaller BML volume compared to other sequences. BML volume was larger when assessed using the contrast enhanced T_1W FS sequence though not statistically significantly different from BMLs when assessed using PDFS and STIR sequences.

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