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Magnetic resonance imaging in osteoarthritis: which method best reflects synovial membrane inflammation?

Correlations with clinical, macroscopic and microscopic features

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Summary

Objectives: : To study synovial membrane (SM) inflammation near the patella with different magnetic resonance imaging (MRI) approaches performed using a T1-injected sequence in knee osteoarthritis (OA), and to compare MRI results with macroscopic, microscopic and clinical findings.

Methods: Fifteen patients fulfilling American College of Rheumatology (ACR) criteria for knee OA and requiring joint lavage completed a functional index (Lequesne's functional index) and a pain visual analog scale (VAS). SM inflammation near the patella was assessed on axial fat saturation post-injected T1 MRI images using three different methods: (1) semi-quantitative score = MRI synovitis score; (2) synovial membrane volume (SMV) analysis; (3) SMV with low (SMVL) ($<0.3\%/s^{-1}$), intermediate (SMVI) ($0.3\%/s^{-1}$ to $1\%/s^{-1}$) and high (SMVH) ($\geq 1\%/s^{-1}$) speed of enhancement. Chondral lesions and SM inflammation were macroscopically graded and SM biopsies performed for microscopic scoring.

Results: All MRI approaches exhibited excellent intra- and inter-observer reproducibility. MRI synovitis score correlated well with macroscopic ($r = 0.61$, $P = 0.003$) and total microscopic scores ($r = 0.55$, $P = 0.03$). Correlations between SMV and macroscopic ($r = 0.60$, $P = 0.02$) and microscopic congestion ($r = 0.63$, $P = 0.01$) were good. SMVH was correlated only with microscopic congestion ($r = 0.79$, $P = 0.01$). Low SMV was associated with neither macroscopic nor microscopic scores. However, it did correlate well with pain-VAS score ($r = 0.61$, $P = 0.03$) and moderately with a functional index ($r = 0.46$, $P = 0.10$).

Conclusion: The three MRI approaches used here provided highly reproducible information on SM inflammation near the patella in knee OA. Compared to SMV, MRI synovitis score seems sufficient to assess synovial inflammation but high SMV is an appropriate indicator of vascular congestion, and low SMV reflects pain in knee OA.

Key words: Osteoarthritis, MRI, Synovial membrane inflammation.

Osteoarthritis (OA), defined by cartilage breakdown and bone modifications, is a chronic disease affecting 8–15% of the populations of developed countries[1,2]. The presence of synovitis is usually considered as a secondary event caused by phagocytosis of cartilage breakdown products but synovitis may also initiate, and contribute to, chondral lesions[3].

Magnetic resonance imaging (MRI) has revealed little about the prevalence of synovial abnormalities in knee OA as most studies have been performed using non-injected images, especially FS T2-weighted images[4–7] which do not distinguish inflamed synovium from fatty tissue. Nevertheless, these studies have shown the prevalence of synovitis to be high, particularly in end-stage disease[6–8]. Contrast agents allow for good characterization of synovium in inflammatory diseases as well as in OA[9–11]. In knee OA, two recent semi-quantitative scoring studies performed with post-injected T1 images confirmed the presence of active synovitis[3,12]. Synovial biopsies performed in only one study showed good correlations between MRI scores and macroscopic and microscopic data[3].

In inflammatory diseases, synovial membrane volume (SMV) is highly correlated with local clinical signs of inflammation[13,14] and histopathologic parameters[10,15–17] in cross-sectional as well as longitudinal studies[18–21]. SM inflammation can also be measured by the speed of enhancement after contrast agent administration[15,17,22]. The

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latter is usually performed on a preselected single sagittal slice, with fast sequences (total acquisition time less than 20 s) repeated over 10 min, which allows the speed of enhancement of the SM at the ROI to be calculated. Results obtained with this method have shown excellent correlation with microscopic inflammatory parameters[15] but are weakly reproducible.

Here, we report the use of a new MRI technique that combines SMV measurement and speed of enhancement of synovial tissue at 186 s in 15 patients suffering from various stages of knee OA. The volume of synovium is determined with low, intermediate and high-speed enhancement and the results are compared with SMV and a semi-quantitative score ''the MRI synovitis score''. The objective of the work is to study synovial membrane (SM) inflammation with different MRI approaches performed using a T1-injected sequence in knee OA, and to compare MRI results with macroscopic, microscopic and clinical findings.

Patients and methods

PATIENTS

MRI was performed in 15 knees of 15 patients (nine women and six men), fulfilling the American College of Rheumatology criteria for knee OA[23]. Patients were scheduled to have joint lavage because of the persistence of pain, chronic joint effusion and/or lack of efficacy of general or local treatments (3 months after corticosteroid or hyaluronate injections on average). Patients were not recruited at the time of surgery and, then, were more representative of the different stages of the disease. Patients with evidence of crystal-induced disease, traumatic injuries or active inflammatory disorders were excluded. The median age of the patients was 58 years (range 40–76). Written informed consent was obtained from all subjects.

ASSESSMENT

Demographic data and other characteristics were recorded at baseline. Functional disability and pain were assessed using Lequesne's functional index[24] and a pain visual analog scale (VAS). Standard blood tests, including serum C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were performed just before arthroscopy. X-rays were graded according to Kellgren and Lawrence[25].

MRI EVALUATION

Technique

All patients underwent MRI between 1 and 7 days before arthroscopic examination. Imaging was performed using a 1.5 T scanner (General Electric Medical Systems, Milwaukee, WI, USA) with a transmit-receive knee coil to achieve uniform receptivity throughout when the knee was in a neutrally rotated position. SM was studied on a fast multiplanar spoiled gradient-recalled acquisition in the steady state T1-weighted sequence (repetition time 180 ms, echo time 4.2 ms, flip angle 90°, field of view 12 × 12 cm, matrix 256 × 256 pixels, slice thickness (ST) 3 mm, slice gap 0.0 mm and 1 nex) performed in a transverse plane without contrast agent. With the patient in the same position, 0.1 mmol/kg of gadolinium-DTPA (Gd-DTPA) (Guerbet, Aulnay, France) was injected into a cubital vein and the sequence was repeated. Total acquisition time for the two sequences was 6 min and 12 s.

SYNOVIAL EVALUATION

SM inflammation was studied with three different methods on the same sequence: (1) a validated semi-quantitative score for the measurement of synovial inflammation in OA ''MRI synovitis score''; (2) quantitative measurement of SMV; (3) quantitative measurements of SMV with low-speed enhancement (SMVL), intermediate-speed enhancement (SMVI) and high-speed enhancement (SMVH) 186 s after Gd-DTPA injection.

Semi-quantitative measurement: MRI synovitis score

Slices chosen to grade SM inflammation corresponded to the first and the last axial slices in which the patella was still visible. SM inflammation was investigated as previously described[3] on an axial post-injection T1-weighted sequence. Briefly, thickening of the inflamed SM was determined in five regions of interest (ROIs) and graded on a four-point scale[3] (Fig. 1). The MRI synovitis score varied between 0 (normal synovial tissue) and 15 (the most severe and diffuse synovial inflammation).

Quantitative measurement of the SMV

SMV[13,26] was measured using image-processing software (MATLAB7) installed on a personal computer (PC). Only those axial slices in which the patella was visualized were selected for volume analysis. The SM was outlined on post-injected images using a threshold of enhancement of 45% between injected and non-injected images[27] (Figs. 2 and 3). The non-synovitis regions were removed and the synovitis area was calculated automatically for each slice. SMV was calculated by summation of the synovitis areas of all slices using the following formula: $SMV = \Sigma(Arsyn_i \times ST)$ where ST is the slice thickness and $Arsyn_i$ is the area of the SM in slice *i*.

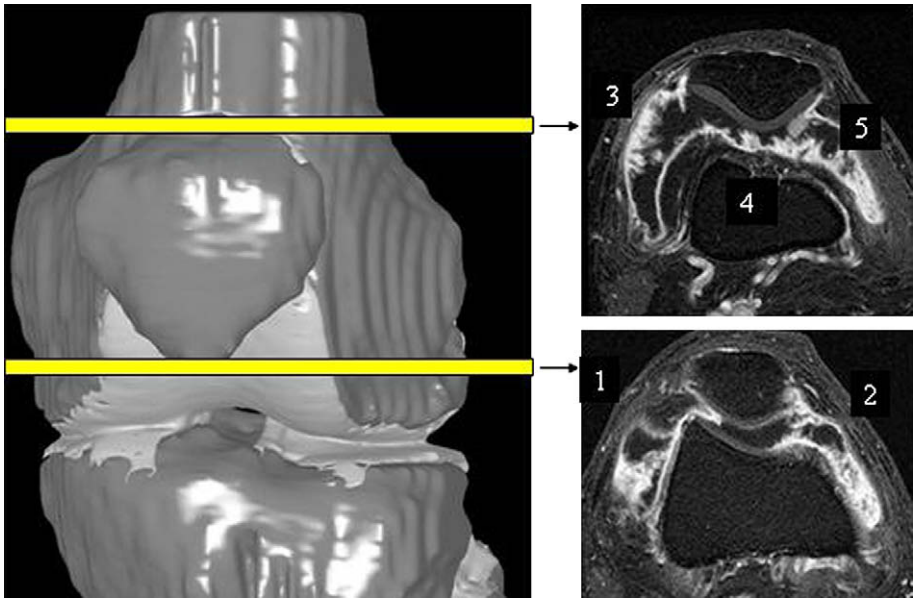

Fig. 1. The two slices chosen for the MRI synovitis score corresponds to the first and the last axial post-injection T1-weighted slices in which the patella was still visible. SM inflammation was graded according to thickening severity in five ROI (1–5). The MRI synovitis score varied between 0 and 15. 254 × 190 mm (72 × 72 DPI).

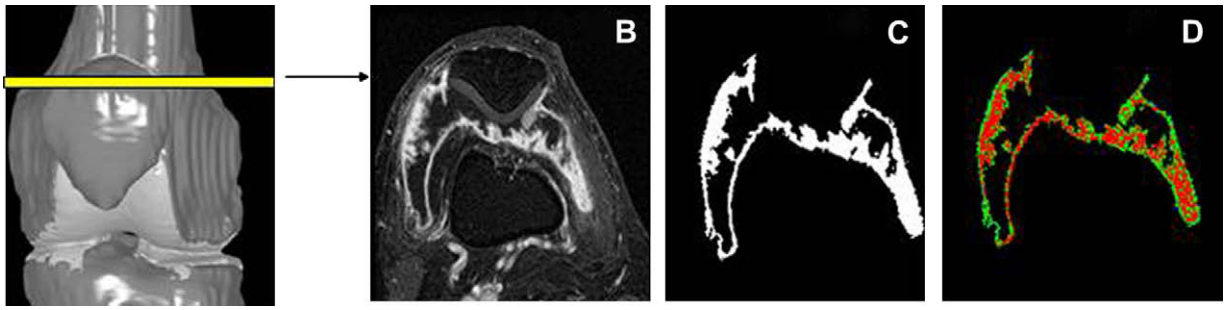

Fig. 2. On axial post-injection T1-weighted slices (B), SM with a threshold of enhancement 45% was outlined (C) and the speed of enhancement was calculated for each voxel and categorized as: low (blue colour) intermediate (green colour), or high speed of enhancement (red colour) 254 × 190 mm (72 × 72 DPI (D)).

Quantitative measurements of SMVL, SMVI and SMVH speed enhancement

The speed of enhancement was calculated for each pixel of the synovitis area outlined according to the following formula: $(S186 - S0)/(S0 \times 186) \times 100$, where signals S186 and S0 were the SM signals at $t = 186$ s and $t = 0$ (before injection). The SMV was assessed according to its speed of enhancement and categorized as: (1) low ($<0.3\%/s^{-1}$), intermediate ($\geq 0.3\%/s^{-1}$ but $<1\%/s^{-1}$) or high speed ($\geq 1\%/s^{-1}$)[15,22,28] (Figs. 2 and 3). The volume of each category and the ratio of SMVH/SMV were also determined.

Magnetic resonance (MR) images were read according to the three different approaches by two observers blinded to the patients' other characteristics. In order to assess inter-observer variability, two observers (ICV and JCG) conducted all 15 examinations. One observer (JCG) made 15 measurements twice to determine intra-observer reproducibility.

CHONDROSCOPIC EXAMINATION

Technique

Chondroscopy was performed under local anesthesia (lidocaine adrenaline 2%) by a rheumatologist (DL). A standard knee arthroscope (2.7 mm) with a 30° fore oblique lens and a wide field of view was inserted *via* the inferior lateral and medial femorotibial portals. Chondroscopic exploration was combined with joint lavage. All procedures were recorded on VHS videotape (super VHS Panasonic VS 100H; Panasonic, Matsushita Electronic industrial, Osaka, Japan). At five regions, three in the suprapatellar recess (lateral recess, medial recess and just above the trochlear groove) and two in the medial and lateral femoral gutter: SM macroscopic analysis and SM biopsies were performed.

EVALUATION OF THE SM (MACROSCOPIC AND MICROSCOPIC SCORING)

The macroscopic appearance of the SM was graded[3] and SM biopsy specimens were obtained when technically possible. SM biopsies were graded for six parameters and a mean total composite score was calculated for each specimen[3,10].

STATISTICAL ANALYSIS

MRI characteristics of SM inflammation were described with medians and ranges. Spearman correlation coefficients (r) were computed to analyse the associations between MRI measures and clinical, biological, macroscopic and microscopic characteristics. An r value lower than 0.3 indicates little or no association, between 0.3 and 0.7 the association is moderate, and above 0.7 it is strong. For SM macroscopic and microscopic data, the average grades at the different biopsy sites on the same knee were calculated. To analyse test–retest reliability, the median and range of the absolute and relative variations between the two observers and between two readings were calculated. Inter- and intra-observer reliabilities of MRI score or volumes were assessed with intraclass correlation coefficients (ICC) derived from a two-way analysis of variance in a random effect model and their 95% confidence intervals (95%CI)[29]. Test–retest reliability was also studied using the Bland and Altman graphical method to check whether reliability errors are homogeneous along the range of score or volume[30]. Statistical analyses were performed using Statistical Analysis System version 9.1 for Windows (SAS institute, Cary, NC, USA).

Results

SAMPLE DESCRIPTION

Characteristics of the study patients, MRI data, and results of histological investigation of the SM are summarized in Table I. Forty synovial biopsies were performed and distributed as follows: two biopsies by knee ($n = 7$), three biopsies by knee ($n = 7$) and five biopsies by knee ($n = 1$). Concerning biopsies localization, 11 were performed in the suprapatellar lateral recess, 11 in the suprapatellar

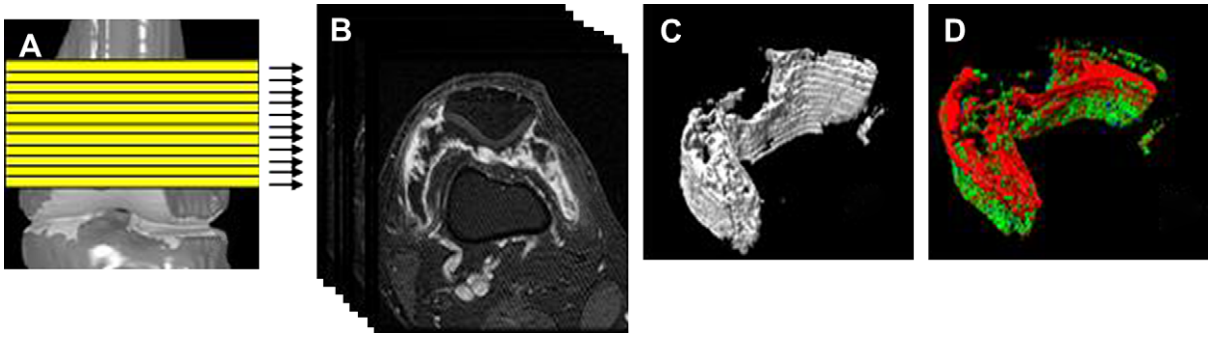

Fig. 3. Only axial post-injection T1-weighted slices in which the patella was visualized were selected for volume analysis (A, B). On each slice, SM with a threshold of enhancement 45% was outlined and the SMV calculated (C). Finally the SMV was assessed according to its speed of enhancement and categorized as: low (blue colour), intermediate (green colour) or high speed of enhancement (red colour) (D). 254 × 190 mm (72 × 72 DPI).

Table I
Clinical, biological, MRI, and arthroscopic characteristics in 15 patients

	Total $N = 15$
	Median (range)
Demographic and clinical characteristics	
Age	58.0 (40.0–76.0)
Sex, *N* (%) – men	6 (40)
VAS pain (0–100)	51.0 (7.0–89.0)
Lequesne's index (0–24)	11.5 (2.0–18.0)
VS (mm/h)	14.0 (1.0–94.0)
CRP (mg/dl)	5.0 (5.0–14.4)
Kellgren grade *N* (%)	
1	1 (8.3)
2	1 (8.3)
3	9 (75.0)
4	1 (8.3)
MRI	
MRI synovitis score (0–15)	8.5 (1.0–13.0)
SMV (mm^3)	4606.2 (139.5–20123.7)
SMVL (mm^3)	1450.5 (24.7–7053.6)
SMVI (mm^3)	2604.8 (69.5–6576.5)
SMVH (mm^3)	786.9 (19.7–13289.2)
SMVH/SMV (%)	17.8 (1.7–66.0)
Macroscopic score	2 (1–3)
Microscopic score	
Synovial lining cells	2 (1–3)
Fibrin deposition	0 (0–3)
Fibrosis	2 (0–3)
Oedema	2 (0–3)
Congestion	1 (0–3)
Infiltration	2 (1–3)
Total composite score	1.5 (0.3–2.3)

medial recess, three just above the trochlear groove, two in the medial femoral gutter and 13 in the lateral femoral gutter.

MRI CHARACTERISTICS OF SM INFLAMMATION

In the total sample, the median MRI synovitis score was 8.5 (range: 1–13) and the median SMV was 4606 mm^3 (range: 139–20124) (Table I). The total SMV comprised 21% SMVH, 48% SMVI and 31% SMVL. The ratio SMVH/SMV was highly variable, ranging from 1 to 66%.

TEST-RETEST RELIABILITY

The relative and absolute inter- and intra-observer variations of the different MRI data are shown in Table II. Inter- and intra-observer reproducibilities were excellent for the MRI synovitis score (ICC = 0.89; 95%CI [0.70–0.96], ICC = 0.95; 95%CI [0.86–0.99] respectively). Inter- and intra-observer reproducibilities were also excellent for SMV, SMVH, SMVI and SMVL (all ICC $\geq$ 0.98). Reliability errors of the different volumes measured were homogeneous along the range of volumes on the Bland and Altman graphic analyses.

ASSOCIATIONS BETWEEN MRI DATA, AND CLINICAL, OR HISTOLOGICAL FINDINGS

Clinical and biological assessment

No correlations between MRI measures and age or biological data were statistically significant. No correlation was noted between MRI synovitis score or SMV and clinical data. Only moderate and positive correlations were noted between SMVL and VAS pain ($r = 0.61$; $P < 0.05$) or Lequesne's index ($r = 0.46$; $P = 0.10$) (Table III). However, although correlation coefficients did not reach statistical significance, SMVH, SMVI and the SMVH/SMV ratio were moderately negatively correlated with clinical characteristics.

Macroscopic and microscopic assessments

MRI synovitis score was positively correlated with the macroscopic appearance of SM ($r = 0.61$), and with congestion ($r = 0.52$) and infiltration ($r = 0.54$) on microscopic analysis performed on 40 SM samples (Table III). Not only SMV and SMVH but also SMVI were correlated with macroscopic ($r = 60$; 0.48 and 0.57 respectively) and microscopic ($r = 0.63$; 0.79 and 0.61) congestion scores. Conversely, SMVL was not statistically correlated with any macroscopic or microscopic score. The correlation between SMVH/SMV and microscopic congestion was positive and statistically significant ($r = 0.63$), whereas that between SMVH/SMV and microscopic infiltration, oedema and fibrosis were moderate and negative. SMVH and SMVI were significantly higher in knees with severe congestion than in knees with mild congestion and were significantly lower in knees with severe fibrosis than in knees with mild fibrosis (data not shown).

Discussion

MRI is known to improve the diagnosis of knee OA when radiographs are still normal, and can help with follow up of disease evolution by facilitating precise assessment of cartilage lesions and measurement of cartilage volume[5,31,32]. However, the role of synovitis on pain and its impact on cartilage breakdown is still debated[4–7]. Moreover, imaging data in OA are rarely compared to histological data which can be considered as the gold standard for synovitis. The aim of this study was to compare three methods of MRI synovitis scoring on post-injected sequence and to compare the results with clinical and histologic data.

Table II
Intra- and inter-observer reproducibility of MRI synovitis assessment

	Inter-observer reproducibility		Intra-observer reproducibility	
	Absolute change	% Change	Absolute change	% Change
	Median (range)	Median (range)	Median (range)	Median (range)
MRI synovitis score	−1 (−3.0; 2.0)	−13.4 (−66.7; 28.6)	0.5 (−2; 2)	10 (−18.2; 33.3)
SMV	−405.6 (−1944.3; 24.8)	−7.1 (−32.7; 16.3)	−7.3 (−253.8; 862.0)	−0.1 (−3.0; 10.4)
SMVL	−171.4 (−1211.7; 106.9)	−13.8 (−54.5; 13.3)	1.3 (−57.3; 382.7)	0.0 (−5.5; 17.1)
SMVI	−152.2 (−705.7; 249.6)	−6.5 (−20.7; 21.2)	−4.0 (−146.4; 452.9)	−0.1 (−3.5; 10.1)
SMVH	−28.2 (−532.0; 53.4)	−4.9 (−51.2; 60.1)	−1.3 (−56.9; 26.4)	−0.4 (−5.9; 20.4)
SMVH/SMV	0.3 (−3.8; 2.9)	4.9 (−13.9; 64.9)	−0.0 (−1.7; 1.8)	−0.3 (−9.6; 12.6)

Table III
Associations between MRI data, clinical, and histologic assessments

	MRI synovitis score (0–15)	SMV (mm^3)	SMVH (mm^3)	SMVI (mm^3)	SMVL (mm^3)	SMVH/ SMV
	r	*r*	*r*	*r*	*r*	*r*
VAS pain score	0.25	−0.09	−0.30	−0.14	0.61*	−0.45
Lequesne's index	−0.11	−0.27	−0.34	−0.30	0.46	−0.39
ESR	0.50	−0.17	−0.33	−0.15	0.21	−0.35
CRP	0.35	0.19	0.04	0.16	0.36	−0.10
SM macroscopic score	0.61*	0.60*	0.48	0.57*	−0.05	0.28
SM microscopic score						
Synovial lining cells	0.16	0.20	−0.05	0.25	−0.13	−0.08
Fibrin deposition	0.35	−0.06	−0.12	−0.10	0.25	−0.17
Fibrosis	−0.01	−0.03	−0.30	−0.08	0.25	−0.37
Oedema	−0.01	−0.01	−0.11	0.00	0.36	−0.34
Congestion	0.52*	0.63*	0.79*	0.61*	0.35	0.63*
Infiltration	0.54*	−0.08	−0.16	−0.12	0.31	−0.34
Total composite score	0.41	0.00	−0.20	−0.01	0.44	−0.48

*$P < 0.05$.

MRI SYNOVITIS SCORE

We confirmed that MRI synovitis score is a simple method of accurately assessing synovial inflammation near the patella in knee OA, requiring no more than 10 min. The superior ROIs are localized near the femoro-patellar compartment while the inferior ROIs is positioned near both femorotibial and femoro-patellar compartments[3]. This score is well correlated with macroscopic and total microscopic scores, congestion and infiltration. As already shown, no correlation was found between this score and clinical characteristics.

SYNOVIAL VOLUME ASSESSMENT

SMV is a more sophisticated method requiring 30 min to accurately assess synovial inflammation in knee OA. This technique has been evaluated mainly in Rheumatoid Arthritis (RA). Similarly to previous studies, synovial volume was studied in a large ROI localized around the patella. The duration of this injected sequence was 180 s – the optimal time when measuring SMV, as 5 min after intra-venous injection, gadolinium leaves the synovium (vessels, interstitial tissue) and diffuses into the synovial fluid[33]. With regard to the segmentation procedure used here, SM outlining was performed with an optimized threshold of enhancement of 45%, as published by Ostergaard[27]. Thus, we demonstrated that SMVs are well correlated with macroscopic and total microscopic scores and particularly with congestion. In comparison to RA the relationships between SMV and clinical signs of inflammation[13,21,22] and histopathologic parameters of synovitis[3,10,17,34] were less strong. As for MRI synovitis score, no relationship was found with clinical or biological data.

VOLUME PLUS SPEED OF ENHANCEMENT OF THE SYNOVIAL TISSUE

We present here an original method of measuring the speed of enhancement of the SM and expressing the result in terms of SMV. SMVL, SMVI and SMVH were automatically acquired with SMV measurement (30 min). So, as previously published in both RA and OA, we applied three thresholds[13,22] based on the speed of SM gadolinium enhancement: first threshold $<0.3\%/s^{-1}$, second threshold $\geq 0.3\%/s^{-1}$ but $<1\%/s^{-1}$; and third threshold $\geq 1\%/s^{-1}$ [13,27]. The speed of enhancement of the SM was determined not only for a ROI on a single slice[15,22] as previously published and which usually exhibited poor reproducibility, but for a large region of SM with excellent intra- and inter-observer reproducibility.

As for SMV, we measured large ranges of SMVH, SMVI and SMVL. As previously demonstrated by Ostergaard *et al.*, the correlation between SMVH and congestion was excellent; however, surprisingly, inverse correlations were found with infiltration, synovial lining cells, fibrosis, fibrin deposits, and oedema[10]. Thus, SMVH seems to be a reliable means of quantifying vascularization in SM and evaluating therapeutic response.

Concerning SMVL, no correlation was found with either macroscopic score or microscopic parameters. However, we demonstrated for the first time a moderate positive correlation between SMVL and VAS pain and Lequesne's index. The relationship does not seem related to inflammatory or a fibrotic pattern, this last parameter being usually linked with disease evolution and joint damage[35]. So, a low level of SM inflammation, without any remarkable microscopic pattern, should be responsible for pain in knee OA. This result could be due to multiple testing, and should be confirmed by a study with a larger sample before adding SMVL to the list of joint features associated with pain in knee OA, such as: bone marrow lesions[36–38], subchondral attrition[39] and periarticular lesions[40].

LIMITS

One limit of this study relates to the use of classic fast multiplanar spoiled gradient-recalled acquisition in the steady state T1-weighted sequence. This restricts the acquisition time to 186 s when it could be less with a fast short imaging sequence or single slice acquisition. Thus, the optimal "time window" of 55 s, classically used to evaluate synovitis in RA was not possible[15]. This can result in an over or underestimation of the rate of enhancement depending on the shape of the enhancement curve. Moreover, SVM was not calculated for the entire knee but only for the region surrounding the patella. The cross-sectional nature of the study does not allow studying the causal relationships of synovitis and chondral lesions and patient symptoms. This question was not under the scope of this work but should be explored in future studies. Finally, the results of this study cannot be generalized to all subjects with knee OA as our sample included patients scheduled to have joint lavage because of the persistence of pain and effusion and lack of efficacy of other treatments.

Conclusion

We demonstrate that both SMV and MRI synovitis score are highly reproducible techniques, but the latter is less time-consuming. As previously published, MRI synovitis score is well correlated with microscopic parameters, especially infiltration score. In comparison to MRI synovitis score, SMV is a time-consuming technique and correlations with microscopic parameters are not improved, except for congestion. As expected, SMVH is highly correlated with vascular congestion but not with clinical

and biological data. We have shown, for the first time, that pain and loss of function may be related to SMVL, which was not associated with any notable microscopic features but this data should be confirmed on a larger sample. We expect that, in future studies, the various MRI methods described here, will provide information about the impact of synovitis on cartilage breakdown, and help accurately assess the impact of drugs on SM inflammation, particularly congestion.

Conflict of interest

None declared.

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