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Anatomical distribution of synovitis in knee osteoarthritis and its association with joint effusion assessed on non-enhanced and contrast-enhanced MRI

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SUMMARY

Purpose: To describe the anatomical distribution of synovitis and its association with joint effusion on non-enhanced and contrast-enhanced (CE) MRI in patients with knee osteoarthritis (OA).
Methods: Baseline MRI was performed at 1.5 T using axial proton density (PD)-weighted (w) fat suppressed (fs) and axial and sagittal T1-w fs CE sequences. Synovial enhancement was scored in nine articular subregions. Maximum synovial enhancement was grouped as absent (0), equivocal (1) and definite (2 and 3). Effusion was scored from 0 to 3 on the axial sequences. We described the anatomical distribution of synovitis, its association with effusion and compared assessment of effusion on T1-w fs CE and PD fs sequences.
Results: 111 subjects were included and examined by MRI. 89.2% of knees exhibited at least one subregion with a minimum grade 2 and 39.6% at the maximum of a grade 3. The commonest sites for definite synovitis were posterior to the posterior cruciate ligament (PCL) in 71.2% and in the suprapatellar region in 59.5% of all knees. On T1-w fs CE, 73.0% of knees showed any effusion. Definite synovitis in at least one location was present in 96.3% knees with an effusion and in 70.0% without an effusion. Higher grades of effusion were scored on the PD fs sequence.
Conclusion: Definite synovitis was present in the majority of knees with or without effusion with the commonest sites being posterior to the PCL and in the suprapatellar recess. Joint effusion as measured on PD fs images does not only represent effusion but also synovial thickening.

Introduction

Osteoarthritic joints regularly exhibit signs of synovial activation even in the early phase of the disease[1–5]. Synovial activation in osteoarthritis (OA) is reflected as synovitis and joint effusion on magnetic resonance imaging (MRI). The amount of synovitis appears to correlate with pain and may be a marker of structural change and clinical outcome[6,7]. The histological correlates of synovitis include synovial hyperplasia, fibrosis, thickening of the synovial capsule, activated synoviocytes and in some cases lymphocytic infiltrates[8].

To date, semi-quantitative MRI assessment of synovitis in large studies of OA is usually performed on non-enhanced fluid-sensitive fat suppressed (fs) sequences[9–11]. Commonly, signal alterations in Hoffa's fat pad are scored as synovitis surrogates[11,12], which have shown an association with pain severity, but have proven to represent only a non-specific marker when using contrast-enhanced (CE) MRI as the reference standard[13]. This seems to be supported by a recent comparative study including histology that found only scoring of T1-weighted contrast-enhanced (T1-w CE) images correlated with microscopically proven synovitis[14]. Consequently, synovitis in osteoarthritic knees should probably be assessed on T1-w CE sequences, which allow evaluation of enhancement and thickening of the synovial membrane[15–17].

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Furthermore, clinical experience has shown that proper differentiation between synovium and joint effusion is only possible on CE images and that fluid-sensitive images seem to over-estimate the amount of intraarticular fluid[18], which is the rationale why some of the available semi-quantitative scoring systems of knee OA suggest a combined synovitis/effusion score for assessing these features on non-enhanced images[9]. Reliable instruments have been introduced recently that are able to assess synovitis in a semi-quantitative fashion at multiple sites within the knee joint on CE images as the site of synovial inflammation seems to be of clinical relevance[19].

To date, it is not known if synovitis is distributed in a homogeneous fashion within the joint or if there are certain anatomical subregions that are affected to a higher degree possibly due to other concomitant intraarticular pathology. Thus, aim of our study was to describe the anatomical distribution patterns of synovial enhancement within the joint cavity and presence of joint effusion in patients with radiographic knee OA based on a comprehensive semi-quantitative scoring system using CE MRI. We further wished to analyze if the amount of joint effusion may be assessed interchangeably on the fluid-sensitive proton density (PD)-w sequence when compared to the T1-w CE sequence.

Material and methods

Subjects

Subjects included in the present analysis were participants of the VIDEO study a double-blind randomized interventional trial of knee OA investigating the symptomatic and structural effects of oral Vitamin D supplementation in participants with knee OA. OA was defined by presence of pain in one knee on most days in the previous month and presence of at least one equivocal osteophyte in the tibio-femoral (TF) compartment [Kellgen–Lawrence (K/L) grade 1].

Patients were recruited through hospital-based clinics, primary care and advertisement in local newspapers. Patients were eligible if aged over 50 years, suffered pain in at least one knee for most days of the previous month, had radiographic evidence of an equivocal osteophyte in the same knee, were ambulatory (i.e., not wheel chair bound) and were able and willing to attend or comply with treatment and follow-up. Patients were excluded if they had secondary OA, septic arthritis, gout, Wilson's disease, Paget's disease, pseudo-gout, a history of inflammatory arthritis or knee stiffness >30 min duration. Further exclusion criteria were current use of cod liver oil or vitamin supplementation with a total Vitamin D content greater than 200 IU, current use of glucosamine or chondroitin for less than 3 months, history of hyperparathyroidism or osteomalacia, current use of anti-epileptic medication, current use of bisphosphonates or use within the last 2 years, history of hypercalcaemia, hypercalciuria, hyperthyroidism, sarcoidosis, renal stones, previous intraarticular injections of steroid within the last 3 months, hyalgan within the last 6 months, previous knee surgery or arthroscopy within the last 6 months, history of an osteoporotic fracture, history of cancer within the last 5 years excluding non-melanoma skin cancer, serious psychiatric disorders including dementia, inability to understand the procedures, inability to attend or comply with treatment or follow-up scheduling and pregnancy.

Altogether, 111 (64.0% female) subjects were examined with MRI at the baseline visit and were included. Mean age was 64.4 years with a median of 64. The age range was from 51 to 81 years. On average the participants were overweight (mean body mass index 29.3, median 28.2, with a range from 21.3 to 42.7).

The study was approved by the local institutional review board.

Radiography

All subjects received weight-bearing conventional radiographs of both knees according to the semiflexed (metatarsophalangeal) radiographic protocol suggested by Buckland-Wright[20]. Knee radiographs were scored by one rheumatologist with 15 years experience in the assessment of knee OA according to the K/L grading scheme[21].

MRI

At the time of the MRI patients were asked to identify their more symptomatic knee whenever both knees had evidence of at least one equivocal osteophyte. 1.5 T MRI of that knee was performed with a phased array knee coil at baseline using the following pulse sequence protocol: sagittal non-fs T1-w spin echo, coronal intermediate-weighted fs, axial PD fs, axial T1-w fs CE and a sagittal T1-w fs CE sequence. For the present study only the axial and sagittal T1-w fs CE (TR 620 ms, TE 15.8 ms, slice thickness/slice gap 4.0 mm/0.2 mm, echo train length 2, field of view 16.0 × 16.0 cm, matrix size 256 × 160, number of signal averages 2) and the axial PD fs (TR 3,860 ms, TE 32 ms, slice thickness/slice gap 4.0 mm/0.2 mm, echo train length 10, field of view 16.0 × 16.0 cm, matrix size 256 × 192, number of signal averages 2) sequences were considered. The CE scans were acquired beginning 3 min after intra-venous (i.v.) injection of 0.2 ml (0.1 mmol)/kg body weight Gadodiamide (Omniscan™, GE Healthcare, Little Chalfont, UK). As both CE sequences required around 4 min scan time, image acquisition of the CE sequences was performed between 3 min and 11 min after i.v. contrast injection. Image assessment of enhancement was performed weeks to months after the images were acquired.

Synovial enhancement was scored semi-quantitatively (SQ) from 0 to 3 according to a recently introduced scoring system by one MSK radiologist with 8 years experience in standardized SQ assessment of knee OA[19]: 0: physiologic enhancement and no synovial thickening, 1: <2 mm (equivocal synovial thickness), 2: ≥2–4 mm (moderate synovitis) and 3: >4 mm (severe synovitis). The following 11 articular subregions were assessed: suprapatellar, infrapatellar, medial parapatellar, lateral parapatellar, intercondylar, around the anterior cruciate ligament (ACL), posterior to the posterior cruciate ligament (PCL), medial perimeniscal, lateral perimeniscal, Baker's cysts and around loose bodies. The remaining sequences of the MRI examinations were not used or displayed for the assessment of synovitis and joint effusion and thus, readers were blinded to these. The reported intra-reader reliability originally performed on 50 knees by the same expert reader used in the present study and a second expert MSK radiologist who is a co-author ranges from 0.67 to 1.00 for the 11 sites[19].

Maximum synovial enhancement was consequently grouped as absent (grade 0), equivocal (grade 1) and definite (grades 2 and 3).

Joint effusion was scored from 0 to 3, separately on the PD fs and T1-w fs CE sequences[9,11]. Effusion was defined as homogeneous hyperintensity within the joint cavity on the PD fs images and as homogeneous intraarticular hypointensity on the T1-w fs CE images. As the descriptions of effusion scoring are based on non-enhanced imaging only, we used a visual subtraction method of the observed amount of capsular distention minus the enhancing synovium within the distended articular cavity to estimate the amount of true hypointense fluid-equivalent effusion on the T1-w FS CE images.

We described the anatomical distribution of synovitis in the whole sample according to subregions and also by effusion status. MATLAB® R2007a (The MathWorks™, Inc., Natick, MA) and Stata® 10.0 (StataCorp LP, College Station, TX) software were used to generate all possible combinations of effusion status and

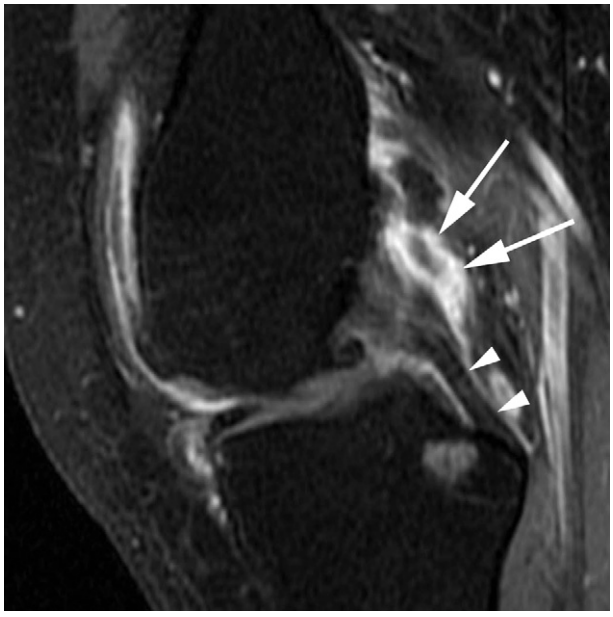

Fig. 1. Localized synovitis. Sagittal T1-w fs CE image shows marked synovial thickening (grade 3) posterior to the PCL (arrows). Distal PCL depicted as hypointense linear structure (arrowheads).

subregions showing the distribution of synovitis across different clusters of subregions. Logistic regression was applied to analyze possible associations between synovitis severity defined by number of affected sites and radiographic disease severity. Scoring of effusion on PD fs and T1-w fs CE sequences was also compared by overall percent agreement and w-kappa statistics.

Results

The baseline K/L grades of examined knees were: K/L 1: 20 knees (18.0%), K/L 2: 42 knees (37.8%), K/L 3: 40 knees (36.0%), K/L 4: 9 knees (8.1%). No knees with K/L grade 0 were included.

Synovitis

99 (89.2%) of knees showed at least one subregion with a synovitis score of 2 or higher and 44 (39.6%) knees exhibited the maximum score of 3 in at least one subregion. The commonest sites of definite synovitis were posterior to the PCL (Fig. 1) in 79 (71.2%) knees and in the suprapatellar region in 66 (59.5%) knees. The prevalence of definite synovitis for the different subregions is visualized in Table I. The mean number of sites showing any synovitis was 6.5 (SD 2.2) for those with K/L grade 1, and 7.6 (SD 2.5), 8.8 (SD 1.4) and 9.2 (SD 1.5) for KL grades 2, 3 and 4. The mean number of affected sites with definite synovitis was 4.2 (SD 2.8), with the median being 4 and a range of 0–11. Definite synovitis in at least one location was present in 96.3% (78/81) of knees with any effusion and in 70.0% (21/30) of knees without an effusion. The anatomical distribution of synovitis for the different subregions and grades for all knees is presented in Table II.

Table II
Anatomical distribution of synovitis

Location	Synovitis grade (%)			
	0	1	2	3
sPat	12 (10.8)	33 (29.7)	50 (45.0)	16 (14.4)
iC	29 (26.1)	42 (37.8)	37 (33.3)	3 (2.7)
iPat	38 (34.2)	43 (38.7)	27 (24.3)	3 (2.7)
pmPat	18 (16.2)	43 (38.7)	37 (33.3)	13 (11.7)
plPat	15 (13.5)	42 (37.8)	37 (33.3)	17 (15.3)
Acl	6 (5.4)	52 (46.8)	48 (43.2)	5 (4.5)
Pcl	4 (3.6)	28 (25.2)	56 (50.5)	23 (20.7)
mMen	21 (18.9)	54 (48.6)	33 (29.7)	3 (2.7)
lMen	28 (25.2)	53 (47.7)	25 (22.5)	5 (4.5)
lB*	n.a.	2 (25.0)	6 (75.0)	n.a.
Bak**	18 (26.9)	32 (47.8)	13 (19.4)	4 (6.0)

* Loose bodies only present in 8/111 knees.
** Baker's cysts present in 67/111 knees.

Using ordinal logistic regression the increasing trend between the number of subregions with synovitis and the KL grades was confirmed with an odds ratio of 1.4 (95% confidence interval 1.2–1.7, $P < 0.001$). However, a moderate and high number of affected subregions were also seen in knees with early TF OA (Table III).

Effusion

The distribution of the different effusion grades for the PD fs and the T1-w fs CE sequence is presented in Table IV. Markedly more knees exhibited a grade 3 effusion on the PD fs sequence when compared to the T1-w fs CE sequence (32 vs 8). Overall agreement of effusion scoring on the PD fs and T1-w fs CE sequence was 65.8%. The weighted kappa comparing agreement between scoring on the PD fs and T1-w fs CE sequences was 0.70 (95% confidence interval 0.62–0.77). Over-scoring of effusion on the PD fs sequence when compared to the T1-w fs CE sequence was observed in 37 cases, over-scoring of T1-w fs CE when compared to the PD fs sequence was only observed in one case where a grade 1 effusion was scored on the enhanced images and a grade 0 on the non-enhanced sequence (Fig. 2). 73.0% of knees showed any effusion on T1-w fs CE and 37.8% of knees exhibited a grade 2 or 3 effusion on the enhanced images. When tabulated against KL grades, the mean score for effusion on the T1-w fs CE images was 0.7 (SD 0.7), 0.9 (SD 0.9), 1.4 (SD 0.8) and 2.4 (SD 0.5) for KL grades 1, 2, 3, and 4 respectively. Using ordinal logistic regression, the increase in the mean effusion score in association to increasing K/L grade had an odds ratio of 3.0 (95% confidence interval 2.0–4.6, $P < 0.001$).

Discussion

In a population of mixed radiographic OA severity, we found that the large majority of knees exhibited definite synovitis in at least one subregion and almost half showed severe localized

Table I
Anatomical distribution of definite synovitis ($n = 111$ knees)

	Location								
Definite synovitis*	sPat	iC	iPat	pmPat	plPat	Acl	Pcl	mMen	lMen
n (%)	66 (59.5)	40 (36.0)	30 (27.0)	50 (45.0)	57 (51.4)	53 (47.7)	79 (71.2)	36 (32.4)	30 (27.0)

Abbreviations: *sPat* – suprapatellar, *iC* – intercondylar, *iPat* – infrapatellar, *pmPat* – peripatellar medial, *plPat* – peripatellar lateral, *Acl* – around the ACL, *Pcl* – posterior to the PCL, *mMen* – perimeniscal medial, *lMen* – perimensical.
* Defined as synovitis grades ≥2.

Table III
Number of subregions with any synovitis according to radiographic OA status

Number of subregions with any synovitis	Radiographic TF OA status				
	K/L 1 $n=20$ (18.0%)	K/L2 $n=42$ (37.8%)	K/L3 $n=40$ (36.0%)	K/L4 $n=9$ (8.1%)	Total $n=111$ (100%)
2–3	4 (20%)	5 (11.9%)	0	0	9 (8.1%)
4–5	0	3 (7.1%)	1 (2.5%)	0	4 (36.0%)
6–7	8 (40%)	8 (19.0%)	5 (12.5%)	1 (11.1%)	22 (19.8%)
8–9	8 (40%)	15 (35.7)	22 (55%)	3 (33.3%)	48 (43.2%)
10–11	0	11 (26.2%)	12 (30%)	5 (55.6%)	38 (34.2%)

synovitis. The commonest site of definite synovitis was posterior to the PCL, which has not been reported previously and is not included in other MRI scoring systems[5,9,16,22]. Surprisingly, also many knees with early OA showed signs of synovitis in multiple articular subregions. Synovitis was also observed commonly in knees with and without concomitant joint effusion. More intraarticular sites affected by synovitis and higher grades of joint effusion are associated with higher grades of radiographic TF OA. Another important finding from this study is that that fluid-sensitive MRI sequences are not able to properly distinguish joint effusion from synovial thickening and therefore commonly over-report the presence of effusion.

Several methods for assessing synovitis with non-enhanced and CE MRI are available[2,6,12]. However, it seems that using a surrogate of synovitis on non-enhanced imaging is a very non-specific measure of synovitis[13]. Based on the experience with assessment of synovitis in rheumatoid arthritis and supported by recent work of Loeuille *et al.*, SQ assessment of synovitis should probably be performed on T1-w CE images, which is the reason to choose a comprehensive whole-joint scoring system based on T1-w CE imaging to assess synovitis in our study[4,14,19].

Unfortunately, we were not able to correlate our imaging findings with a gold standard such as histology. However, previous studies confirmed the association of synovial thickening observed on T1-w CE MRI with histologically proven synovitis and validated the use of MRI as a non-invasive, sensitive method for evaluating synovial membrane changes[4,14]. A drawback is the missing correlation of our findings with measures of pain, which would have gone beyond the scope of this report. Another shortcoming is the missing information on prior knee trauma. Knee trauma may lead to an acute inflammatory response and is usually cause of joint effusions. Remote trauma may be a trigger of secondary intraarticular damage that may result in synovial activation.

We chose the start of the T1-w fs CE sequence at 3 min after i.v. contrast administration according to the literature applying static CE MRI to large joints in OA research[5,13,16]. As we did not attempt to investigate the dynamic enhancement over time, there might be the possibility of over- (due to diffusion of contrast material into the joint cavity) or under-estimation (due to early start of the sequence) of the amount of synovitis. Dynamic contrast enhanced imaging might play a much greater role when evaluating the effect of disease-modifying OA drugs over time[14,23,24].

Table IV
Joint effusion on non-enhanced and CE imagings

Sequence T1-w fs CE	PD fs				
	0	1	2	3	Total
0	28	2	0	0	30
1	1	24	11	3	39
2	0	0	13	21	34
3	0	0	0	8	8
Total	29	26	24	32	111

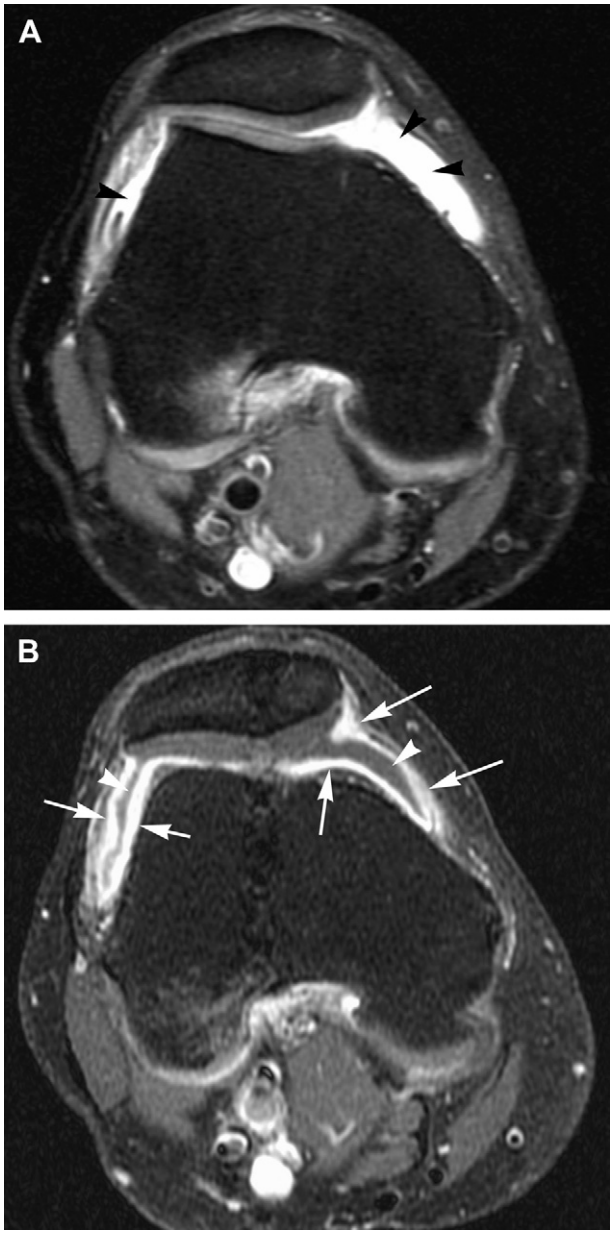

Fig. 2. Joint effusion. (A) Axial PD fs image. Marked bright signal intensity within the joint and convexity of the joint capsule suggestive of a large joint effusion are depicted (arrowheads). (B) Axial T1 fs CE image of the same knee at the same slice position. The CE image shows marked synovial thickening depicted as hyperintense tissue lining along the joint capsule. Only a small amount of effusion is observed (arrowheads).

The commonest site of definite synovitis was posterior to the PCL, a finding that has not been reported previously. The intercondylar notch seems to play an important role for joint integrity. Around 20% of subjects with knee OA exhibit ACL disruptions without recalling trauma to the knee joint, which seems to represent an independent risk factor for consequent cartilage loss[25]. Recent work by Stein *et al.* from the Osteoarthritis Initiative found a strong association of femoral notch stenosis with prevalent ACL tears cross-sectionally[26]. Chronic friction within the notch might lead to debris and detritus triggering localized periligamentous synovitis around the ACL and PCL[27]. Pathology of the PCL and its relation to disease activity and progression has not been explored

in detail. Localized synovitis has been recognized by several authors, but to date most of these investigations focused on Hoffa's fat pad or the perimeniscal regions[5,12,13].

Joint effusion is a reflection of synovial activation and often observed in conjunction with differing grades of synovitis. Surprisingly, we found that 70% of knees exhibited definite synovitis in at least one subregion despite absent joint effusion. This finding supports that localized synovitis might be more common than previously thought, but may not necessarily suffice to trigger relevant joint effusion. In knees without OA an association of meniscal damage and joint effusion could be shown, although that study did not explore the role of concomitant localized synovitis[28].

A large multicenter study based on ultrasound reported joint effusion in about 30% without signs of synovitis[29]. To date only one study assessed the possible role of CE ultrasound for assessment of synovitis in knee OA. The authors reported a comparable sensitivity for the detection of effusion and synovitis in the superior recess of the knee[30]. If CEUS yields comparable results concerning whole knee assessment remains to be proven in future studies. However, CEUS seems to be suited to track treatment response over time by evaluating changes in synovial perfusion in selected parts of the joint as has been shown for rheumatoid arthritis[31].

Commonly, joint effusion is assessed SQ on axial fluid-sensitive images[9,11] where fluid-equivalent signal within the joint cavity is thought to represent effusion. Our results suggest that fluid-sensitive sequences are not able to properly distinguish between joint fluid and synovial thickening and that the amount of fluid is commonly over-estimated as both, joint effusion and synovitis, are depicted as hyperintense structures not distinguishable from each other. For this reason some authors suggested a combined score of assessing joint effusion and synovitis[9]. As a consequence, we believe that the amount of joint fluid should ideally be assessed on T1-w CE sequences whenever possible.

Summarizing our findings, we found that MRI-assessed definite localized synovitis is very common in knees with OA and is also commonly found in joints without exhibiting concomitant joint effusion. More severe synovitis, defined by the number of affected intraarticular sites, and higher grades of joint effusion are associated with radiographic OA severity in a linear fashion. Joint effusion seems to be over-estimated on fluid-sensitive MRI sequences as these cannot distinguish fluid from the synovial membrane and thus, effusion should be assessed on T1-w CE images whenever possible. The clinical consequence of synovial enhancement at the different anatomical sites and its relation to joint effusion and structural progression needs to be further explored in longitudinal investigations.

Authors' contributions

Conception and design of the study: Nigel K Arden, Leonard King, Richard Keen.

Analysis and interpretation of data: Matthew Thomas, Amit Kiran, Nigel K Arden, M Kassim Javaid, Frank W Roemer.

Collection and assembly of data: Leonard King, Richard Keen.

Manuscript preparation: Frank W Roemer, M Kassim Javaid, Ali Guermazi.

Critical revision of the article for important intellectual content: All authors.

Final approval of the article: All authors.

Conflict of interest

Ali Guermazi is president of Boston Imaging Core Lab, LLC (BICL), Boston, MA, a company providing radiological image assessment services. He is consultant for Merck Serono, Facet Solutions, and Stryker and receives research grant from General Electric.

Frank Roemer is partner and vice-president of BICL.

None of the other authors have declared any possible conflict of interest.

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