CHAPTER 8

EVOLUTION OF SYNOVITIS IN OSTEOARTHRITIC KNEES AND ITS ASSOCIATION WITH CLINICAL FEATURES

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ABSTRACT

Objective: To investigate the course of synovitis on contrast-enhanced MRI In osteoarthritic knees over 2 years, and its association with pain and cartilage deterioration.

Methods: Consecutive patients (n=39, mean age 61 years, 79% woman, median (range) BMI 29 (24-48) kg/mm^2) with clinical OA were included. Baseline and follow-up contrast-enhanced MR images (3T) were scored paired in chronological order for synovitis (semi-quantitatively at 11 sites (range 0-22)), cartilage deterioration and bone marrow lesions (BML) (semi-quantitatively according to KOSS). Changes in sum scores were calculated. Cartilage deterioration was defined as change of ≥ 2 above the smallest detectable change (SDC). Pain was assessed by standardized questionnaires. Logistic and linear regression models were used to investigate association between synovitis change and cartilage deterioration and between synovitis change or cartilage deterioration and change in pain.

Results: The total synovitis score did not change over 2 years (mean change 0.2 (SD 3.2), although changes in individual patients were observed. Cartilage deterioration was observed in 51% of patients. Increase in synovitis score was significantly associated with cartilage deterioration, independently of BML change (adjusted OR (95% CI) 1.3 (1.004-1.8). Change in synovitis was not associated with change in pain, whereas cartilage deterioration was associated with change in ICOAP constant pain in adjusted models (OR (95%CI) 2.8 (0.4-5.3).

Conclusion: In individual patients synovitis fluctuates during disease course. Increase in synovitis is associated with cartilage deterioration, suggesting a role for synovitis as a target for disease-modifying treatment.

INTRODUCTION

The disease course of osteoarthritis (OA) in the knee is known to be variable; some patients are known to progress rapidly while others remain stable over a long time[1,2]. However, which processes underlie these differences in disease course remain unknown.

Although OA is considered a non-inflammatory condition, synovial inflammation is prevalent[3] and could play an important role in the pathophysiology of the disease[4]. However, to investigate synovitis in knee OA patients a valid method to assess synovitis is necessary. Currently, the gold standard for assessing synovial inflammation is based on histological analysis of synovial biopsy samples, a methodology that is not patient friendly and technically difficult. Alternatively synovitis can be assessed by contrast enhanced (CE) MRI. It has been proven to be a practical and reliable alternative in evaluating synovitis in knee OA patients[5-12]. As synovitis is known to be patchy and heterogeneous[11], a synovitis scoring method on MRI should encompass a sufficient number of compartments. The synovitis scoring method developed by Guermazi et al.[13] is a comprehensible and practical method, which meets these requirements and compares well with synovial inflammation in tissue biopsies of knee OA patients[8].

The importance of synovitis in knee OA has been supported by several MRI studies that showed an association of synovitis with cartilage deterioration[14-17] and pain[12,18]. Nevertheless, very few studies investigated changes in synovitis over time[19,20] and these indicated an association with pain, but not with cartilage deterioration. However, in these studies no contrast enhancement was used, which precludes a precise determination of synovitis. Therefore, the evolution of synovitis during the disease course and its role in cartilage progression and change of pain in knee OA patients remains unclear.

Therefore, in the present study, we aimed to investigate the change of synovitis on contrast Gd-chelate-enhanced MRI over 2 years and its association with cartilage deterioration and change in pain in knee OA patients.

METHODS

Study design

This study is part of the ongoing geMstoan study (GEneration of Models, Mechanism & Markers for STratification of OsteoArthritis patieNts)[8], a cohort study in established and end-stage knee OA patients to find new biomarkers for OA progression. This study has been approved by the ethics committee of the Leiden University Medical Center (LUMC). All patients provided written informed consent.

Patients

Between 2008 and 2013, patients with symptomatic radiographic primary knee OA, according to American College of Rheumatology (ACR) criteria,[21] attending the rheumatology or orthopaedic department of the LUMC or orthopaedic department of the Diaconessenhuis, Leiden, were included. The geMstoan study comprises two groups of patients based on their clinical status; one with end-stage disease who received a total knee arthroplasty and the other group with a mild to established OA, with no indication for an arthroplasty. For the current analysis patients with mild to established OA were investigated. Patients with other rheumatic diseases, using immunosuppressive drugs or having knee injections (i.e. corticosteroids) in the past 3 months were excluded. Patients with chronic renal insufficiency (Cockroft-Gault < 60 mL/min) did not undergo Gd-chelate enhanced MRI.

MRI acquisition

We used a 3T Philips Achieva MR system (Philips Healthcare, Best the Netherlands) with an 8-channel dedicated knee coil. Coronal and sagittal proton density (PD) fast spin-echo (FSE) driven equilibrium images were obtained with a field of view (FOV) of 150X 150 mm, an acquisition matrix of 304X 240, and slice thickness of 3 mm., repetition time (TR) was 3000 ms; echo time (TE) 34 ms. Axial and coronal frequency selective fat suppressed PD FSE images were obtained with the same geometric parameters, and TR of 2675, TE 24. A T1-weighted axial sequence with TR 581 ms, and TE 20 ms was obtained with slice thickness of 3.3 mm, FOV 160. The sixth sequence was a sagittal three-dimensional (3D) T1-weighted spoiled gradient echo (GE) frequency selective fat-suppressed sequence with TR 16,3; TE 9.2; flip angle 35°; 1.5 mm slice thickness; FOV 150x150; 304x304 acquisition matrix. Finally contrast enhanced (CE)-MR images were obtained following injection of gadoterate meglumine (0.2 ml/kg) (Dotarem; Guerbet) in the cubital vein using a power injector (Medrad) with a rate of 2 ml/second followed by a 40-ml saline flush also at a rate of 2 ml/second. We subsequently obtained frequency selective fat suppressed T1-weighted, FSE with TR of 655 ms, and TE of 20 ms, in both the axial and sagittal planes

MRI scoring

Cartilage was assessed on PD-FSE and GE images. BML were scored using the fat suppressed PD-FSE and GE images. Synovial tissue was assessed on the Gd-chelate enhanced images[8,22,23]. All MRIs were scored in paired samples in a chronological order. Synovitis was scored in a semi-quantitative way at 11 different sites according to Guermazi et al.[13]. Synovial thickness was measured and scored as followed: 0, when synovial thickness was less than 2 mm, 1 when thickness was between 2-4 mm and 2 when synovial thickness was above 4 mm. The total synovitis score of 11 sites was calculated (range 0-22). A total score of 0-4 was considered normal (no synovitis); 5-8 represents a mild, 9-12 a moderate and above 13 a

severe synovitis[13]. Intra-class correlation (ICC) was based on a random sample of 10% Gd-chelate enhanced MR images and was 0.93 for synovitis and 0.90 for synovitis change.
Cartilage damage and bone marrow lesions (BMLs) were scored according the Knee Osteoarthritis Scoring System (KOSS) score in 9 compartments, as described elsewhere[22]. In short, cartilage damage was defined as a combination of diffuse and focal cartilage defect (0 = absent (no abnormality in signal intensity or morphology), 1 = less than 50% reduction of cartilage thickness, 2= 50% or greater reduction of cartilage thickness, grade 3= full-thickness or near-full-thickness cartilage defect). To investigate cartilage damage throughout the whole knee diffuse defects (0-27) and focal defects (0-27) were summarized, creating a total cartilage damage score (possible range 0-54). Subsequently, change in summarized cartilage damage scores between two time points was defined as cartilage deterioration. ICC for total cartilage score was 0.96 and ICC for cartilage deterioration was 0.73. Cartilage deterioration was defined based on the smallest detectable change (SDC), being measurement error; a change in the summarized score of cartilage defects ≥ 2 was used to define cartilage deterioration. Cartilage deterioration was used as dichotomous variable. BMLs were defined as an ill-defined area in the subchondral bone extending from the articular surface and were graded from 0-3 (0= absent, 1= minimal < 5 mm, 2 = moderate 5-20mm, 3= severe ≥ 20mm). BML scores were summarized (range 0-27) to reflect BMLs throughout the knee. Subsequently the change in total BML scores between time points were calculated and defined as change in total BML score. ICC was 0.98 for total BML scores and 0.57 for change in total BML scores.
All MRI were analyzed by one experienced reader (BdL). Scoring was done after extensive learning sessions and under supervision of an experienced musculoskeletal radiologist (JB). During the assessment, the reader was blinded to radiographic results and patient data.

Scoring knee radiographs:
Baseline radiographs (posterior anterior (PA) fixed flexion) were obtained of all patients. Radiographs were scored, blinded for patient characteristics, by an experienced musculoskeletal radiologist (HK), with 30 years of experience in scoring musculoskeletal radiographs, according to the Kellgren- Lawrence (KL) scale[24]. Reproducibility was good as described elsewhere[8].

Clinical data
In the geMstoan patients demographics and disease characteristic were collected via standard questionnaires. Measurement of pain in the imaged knee was achieved by using three questionnaires that each investigates different dimensions of pain. General assessment of self-reported pain was assessed by the visual analogue scale (VAS, 0-100). The VAS is a one-dimensional measure of pain intensity. A score of 100 represents worst

possible pain intensity. The measure of Intermittent and Constant OsteoArthritis Pain (ICOAP)[25] was filled in to assess constant pain and intermittent pain. Higher scores indicate worse pain experience. The Knee injury and Osteoarthritis Outcome Score (KOOS subscale pain, 0-100)[26] was used. In contrast to all other scales a score of 0 represents worst possible pain. Patients were asked to fill in both KOOS and ICOAP questionnaire for pain experienced in the last 7 days. For analysis change in pain was used.

Statistics

Normal distributed variables are depicted as mean (standard deviation), otherwise as median (range). For comparison between time points, paired sample t-test was used for all variables except for cartilage deterioration for which Wilcoxon signed rank test was used and comparison of NSAID use for which Chi-squared test was used. Depending on normal distribution of the data, comparison of the sample of patients used in the follow-up analysis with the original baseline patient population, independent t-test was used for age, Mann-Whitney U tests were used for BMI and KL grade and Chi-squared test was used for gender. To investigate the association of synovitis change with cartilage deterioration both unadjusted as well as adjusted logistic regression models were performed. To investigate the association of synovitis change with pain both unadjusted and adjusted linear regression models were performed. Statistics were calculated by SPSS 20.0 (IBM, Armonk, NY).

RESULTS

Patient characteristics

Of 62 patients at baseline, one patient developed after one year an Anti-cyclic Citrullinated Peptide (anti-CCP)-antibody positive, rheumatoid factor positive oligoarthritis and was excluded from the study, resulting in 61 patients at baseline (mean (SD) age 61.5 (6.9) years, 79.5% woman, BMI median (range) 28.6 (22.8-47.8) kg/mm^2, median (range) KL score 2 (0-4)) included in the geMstoan study. Thirty nine out of these 61 patients had Gd-chelate enhanced MR images at both baseline and follow-up that has been used for current analysis (Figure 1). These 39 patients did not significantly differ from the original 61 patients at baseline in age, gender, BMI or KL grade (data not shown). Patient characteristics and MRI features are displayed in Table 1. Gd-chelate administration was well tolerated by all patients.

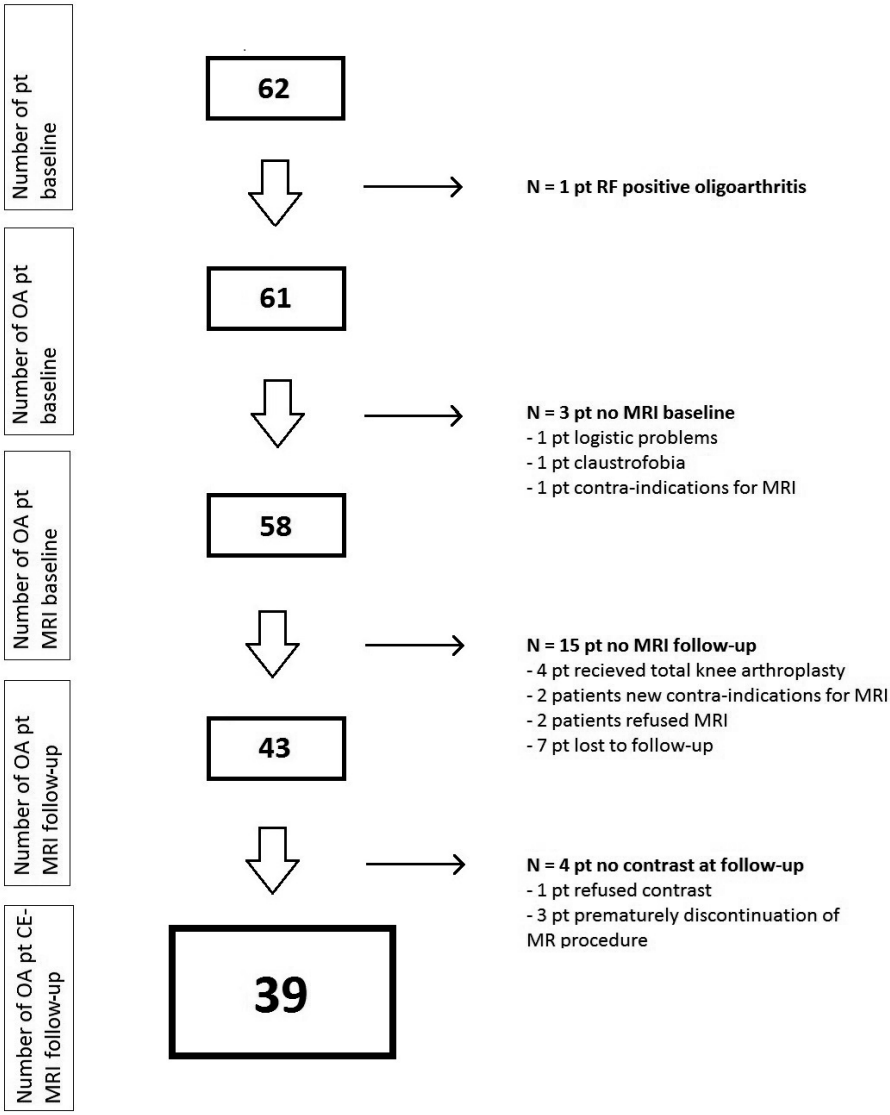

Figure 1. Flowchart of patients available for current analysis. Abbreviations: RF = rheumatoid factor, OA = osteoarthritis, pt =patients, N = number, MRI = magnetic resonance imaging, CE = contrast-enhancement

Table 1 Patient characteristic 39 patients

	Baseline	2 years follow-up	Difference	p-value
Age	61.1 (6.7)	-	-	-
Gender, n (%)	31/39 (80%)	-	-	-
BMI*	28.8 (23.3-47-8)	-	-	-
KL grade*	2 (0-4)	-	-	-
NSAID, n (%)	17/38 (45%)	12/38 (32%)	- 5 (13%)	0.065
ICOAP constant pain (0-100)*	25 (0-75)	15 (0-75)	-8.1 (21.0)	0.028
ICOAP intermittent pain (0-100)	35.9 (24.9)	28.2 (20.2)	-7.6 (20.2)	0.030
KOOS pain (0-100)	61.4 (23.2)	63.2 (21.7)	1.7 (14.0)	0.465
VAS pain* (0-100)	42 (0-96)	29 (0-87)	-6.2 (20.6)	0.069
Total synovitis score on MRI (0-22)	5.59 (2.3)	5.74 (2.9)	0.15 (3.2)	0.764
Cartilage deterioration on MRI (0-54)*	16 (4-37)	20 (4-37)	2 (-1 -11)	< 0.001
Total BML score on MRI (0-27)*	4 (0-11)	5 (0-12)	0.3 (1.8)	0.299

*Mean (SD) are given except for variables that were not normal distributed (median (range)), indicated with a *, for gender and NSAID use number (%) is given. Abbreviations: n = number, BMI = body mass index, KL = kellgren and Lawrence, ICOAP = measure of Intermittent and Constant OsteoArthritis Pain, KOOS = Knee injury and Osteoarthritis Outcome Score,VAS = visual analogue scale, CE-MRI = contrast enhanced Magnetic resonance images, BML = bone marrow lesions*

Course of synovitis, cartilage damage and BMLs over a 2-year period

The mean follow-up time was 2 years and 3 months. A mild synovitis in the knees was observed that did not change over time: the mean (SD) total synovitis score at baseline was 5.6 (2.3) and was similar at follow-up (5.6 (2.9)) (Table 1). However, changes were seen on individual levels, illustrated by Figure 2 and Figure 3A. Figure 2 shows synovitis scores per anatomical site at baseline and follow-up. Synovitis (score 1 or 2) was most frequently present at the medial parapatellar site (in 31 and 33 patients at baseline and follow-up visits respectively), adjacent to the posterior cruciate ligament (PCL) (in 30 patients at baseline and in 28 patients at follow-up) and at the suprapatellar site (in 22 and 24 patients at baseline and follow-up respectively). The site adjacent to the PCL was most frequently displaying the maximal score of 2 at both baseline (n= 8) and follow-up (n=9). Loose bodies, and therefore synovitis surrounding loose bodies, were not seen in any patient at both baseline and follow-up. When the 11 sites were investigated separately over time, the sites that most frequently displayed synovitis at baseline were also the sites that most frequently showed changes over time (39 % of patients in both medial and suprapatellar site and 44 % at the site adjacent to PLC). In contrast, patients who displayed no synovitis at a particular site at baseline often did not display synovitis at 2-year follow-up either (69% of patients at the Bakers' cyst site and 72% of patients at the intercondylar site did not show synovitis at both baseline and follow-up).

Subsequently, we investigated the change in total synovitis scores on individual patient level. Figure 3A shows distribution plots for change in total synovitis score over a 2-year period. This figure clearly shows that the change in total synovitis score varies between patients, which is also reflected by its range (-7 till 9).

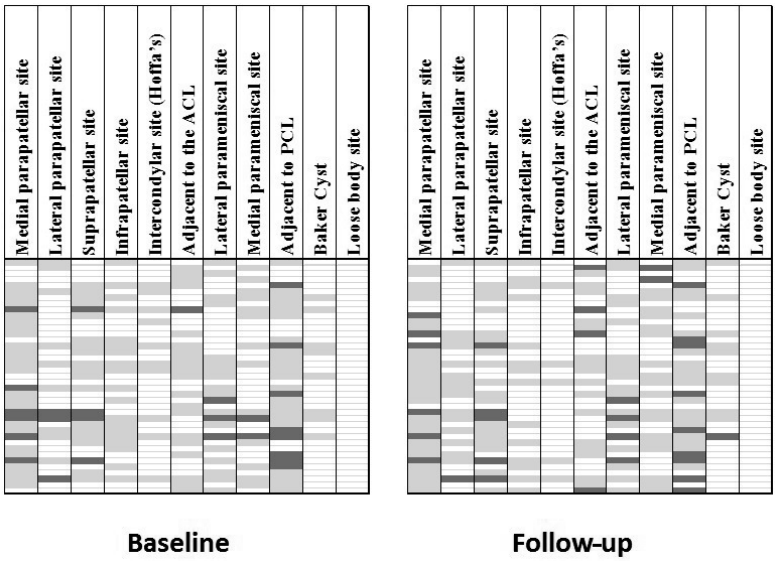

Figure 2. Total magnetic resonance imaging scores of synovitis at 11 sites of the whole knee joint in knee osteoarthritis patients at baseline and follow-up visit. Each row represents 1 patient; the baseline patient row corresponds to the follow-up patient row. Columns represent the 11 different synovitis sites. The score range was 0–2: 0 =white, 1 = light gray, 2 = dark gray. Abbreviations: ACL = anterior cruciate ligament, PCL = posterior cruciate ligament.

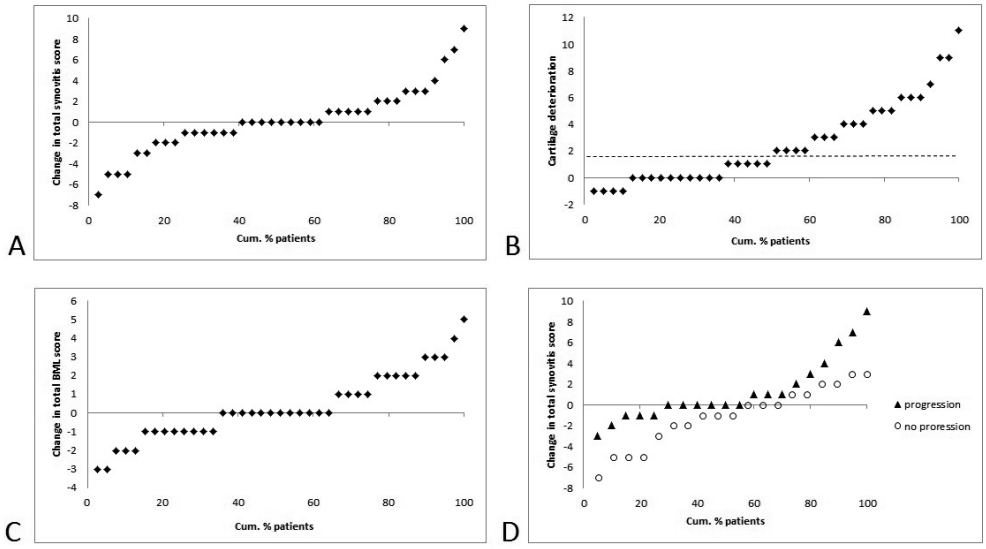

Figure 3. Cumulative probability plots of change in total synovitis score, change in total BML score, cartilage deterioration and for change in total synovitis score stratified for cartilage deterioration progression in all knee osteoarthritis (OA) patients over 2-year period. **A.** Change in total synovitis score. **B.** Cartilage deterioration. The dotted line represents the smallest detectable change (SDC). Patients above the dotted line were classified as having cartilage deterioration progression. **C.** Change in total BML score. **D.** Change in total synovitis score stratified for cartilage deterioration progression.

Relation of synovitis change and change of BMLs with cartilage deterioration

Cartilage deterioration significantly increased over time (Table 1 and Figure 3B). Figure 3B shows that 20 patients (51%) had cartilage deterioration over 2 years (the dotted line represents the SDC of 1.95). Cartilage deterioration was seen in 17 (43.6%) patients in the patellofemoral joint and in 17 (43.6%) patients in the tibiofemoral joint, and was more frequent in the medial compartment compared to the lateral compartment of the tibiofemoral joint (35.9% versus 20.5%). The fluctuating nature of BMLs over time is underscored by the change in total BML scores that ranges from -3 till 5. The large variety in change in BML scores between patients is illustrated by Figure 3C.

Figure 3D shows that patients with cartilage deterioration had on average an increase in total synovitis score over time (positive mean (SD) total score 1.3 (3.1)), while patients without cartilage deterioration had on average a decrease in total synovitis score over time (negative mean (SD) -1.1 (2.9)). The difference in change in total synovitis scores between patients without cartilage deterioration and with cartilage deterioration was statistically significant (difference (95% CI) (-2.4 (-4.3 till -0.4)).

To further investigate the association between change in total synovitis score and cartilage deterioration we adjusted for other variables in logistic regression analyses. A statistically significant association was observed between change in the total synovitis score and cartilage deterioration, taking into account the change in the total BML score (OR (95% CI) 1.3 (1.004-1.772). The effect size of the association increased when correcting for baseline characteristics, although the statistical significance was lost (Table 2).

Table 2: The association between change in total synovitis score and change in total bone marrow lesion (BML) score over 2-year period with cartilage progression in 39 patients with knee osteoarthritis.

	OR (95% CI)	p-value
Synovitis change	**1.3 (1.022-1.774)**	**0.035**
BML change	1.3 (0.865-1.816)	0.232
Synovitis adjusted for BML	**1.3 (1.004-1.772)**	**0.047**
Synovitis adjusted for age, gender and BMI, BML	***1.4 (0.981-1.858)***	***0.066***

Abbreviations: BML = bone marrow lesions, BMI = body mass index, OR = odds ratio, CI = confidence interval. P- value < 0.05 was considered significant (bold), P-value < 0.10 was considered a trend (bold and italic). Maximum synovitis score at 11 anatomical areas is 22

Relation of synovitis change, cartilage deterioration and change in BMLs with change in pain

At follow-up, significantly less pain was reported for both subscales of the ICOAP and a trend for less pain was reported for the VAS pain (Table 1). To investigate the associations of several MRI features with pain linear regression models were used (Table 3). Although in univariate analyses associations were suggested for change in the total synovitis score or change in the total BML score with change in pain over the 2-year period, these

associations were lost when adjusted models were used. Cartilage deterioration was found to be associated with change in pain and the association with change in ICOAP constant pain remained statistically significant even in adjusted models (B (95%CI) 2.8 (0.4-5.3)). Additional adjustment for baseline variables (age, gender and BMI), showed similar results; only cartilage deterioration was significantly associated with change in ICOAP constant pain over time (B (95%CI) 3.1 (0.5-5.7)).

Table 3: The association between change in total synovitis score, change in total bone marrow lesion score and cartilage deterioration over 2-year period with change in pain in knee osteoarthritis patients.

	ICOAPc B (95% CI)	ICOAPi B (95% CI)	KOOSp B (95% CI)	VAS B (95% CI)
Change in total synovitis score, crude	1.7 (-0.6-3.9)	***2.0 (-0.1-4.1)***	-1.1 (-2.6-0.4)	***2.0 (-0.02-4.1)***
Change in total synovitis score, adjusted*	0.3 (-2.2-2.8)	1.1 (-1.4-3.6)	-0.3 (-2.1-1.4)	0.9 (-1.5-3.2)
Cartilage deterioration, crude	**3.0 (0.9-5.1)**	**2.3 (0.2-4.5)**	**-1.6 (-3.1- -0.1)**	**2.1(0.005-4.2)**
Cartilage deterioration, adjusted *	**2.8 (0.4-5.3)**	1.8 (-0.7-4.2)	-1.4 (-3.2-0.3)	1.5 (-0.9-3.8)
Change in total BML score, crude	0.8 (-3.2-4.8)	1.4 (-2.5-5.2)	-0.9 (-3.6-1.8)	**3.7 (0.1-7.3)**
Change in total BML score, adjusted*	0.1 (-3.8-3.9)	0.5 (-3.3-4.3)	-0.4 (-3.2-2.3)	3.0 (-0.7-6.6)

** adjusted for other two change parameters. Abbreviations: ICOAP = measure of Intermittent and Constant OsteoArthritis Pain, ICOAPc = subscale constant pain, ICOAPi = subscale intermittent pain, KOOSp = Knee injury and Osteoarthritis Outcome Score subscale pain, VAS = visual analogue scale for pain, BML = bone marrow lesions. P-value < 0.05 was considered significant (bold), P-value < 0.01 was considered a trend (bold and italic)*

DISCUSSION

To our knowledge this is the first study that investigates synovitis change over 2 years using CE-MRI. We found that synovitis was most frequently seen at the medial parapatellar and the suprapatellar sites and at the site adjacent to posterior cruciate ligament (PCL). Over a 2-year period the total amount of synovitis in the osteoarthritic knees was relatively stable on group level, although fluctuations were seen on individual level. An increase in synovitis severity was significantly associated with cartilage deterioration over time. Although in univariate analyses an association of change in total amount of synovitis in the osteoarthritic knee with a change in pain was seen, this association was lost after adjustment. Also a change in the total amount or size of BMLs in the osteoarthritic knee was not associated anymore with change in pain after adjustment. Cartilage deterioration over 2 years was associated with change in pain, also taking in account changes in the total amount of synovitis and BMLs in the osteoarthritic knee.

In the present study increase in synovitis in the whole knee was associated with cartilage deterioration and only in unadjusted models with increase in pain. This is in contrast with two studies that suggested a role for synovitis in the increase in knee pain, not in

cartilage progression[19,20]. This discrepancy could be explained by a number of reasons. First, both previously reported studies used signal changes in Hoffa's fat pad on non-CE MRI as surrogate for whole knee synovitis, while in the present study Gd-chelate enhanced images were used. Past studies have shown that signal changes in Hoffa's fat pad detected on non-CE MRI are not specific for synovitis in the knee. Therefore, findings reported in these studies could be a reflection of other processes in the knee instead of synovitis[9,27]. Second, both studies used a synovitis sum score that was composed of a limited number of anatomical sites in the knee, while in the present study the total synovitis score according to Guermazi et al.[13], encompassing 11 different sites throughout the whole knee, was used. In the present study the total synovitis score was especially influenced by the suprapatellar site (synovitis change frequently observed) and not by the two other sites (the infrapatellar site and intercondylar site), investigated by the studies by Hill et al. and Zhang et al.. In accordance with this explanation Hill et al. did not find an association of synovitis at the suprapatellar site with VAS pain. Finally, both studies adjusted for baseline cartilage scores but not for cartilage deterioration in their investigation with pain. In our study cartilage deterioration was significantly associated with pain and adjusting for cartilage deterioration led to the loss of association of synovitis change with change in pain. Therefore, cartilage deterioration could serve as mediator in the association between synovitis and pain, explaining differences with earlier literature.

In our study the mean total synovitis score at group level was almost the same between baseline and follow-up, while overall pain was less frequently reported at the follow-up visit compared to the pain score at baseline. These observations were also described by Kortekaas et al. who investigated synovitis change using ultrasound in patients with hand OA[28]. Decrease in pain could be explained by the fact that at time of inclusion patients consulted their physician because they had a health problem, which is most frequently due to pain. After 2 years these patients are more likely to have accepted diagnosis, have adapted expectations and have received treatment, resulting in a subjective pain reduction[29,30]. An alternative explanation is that the decrease in pain is a result of a statistical phenomenon called regression to the mean. Future longitudinal studies investigating pain over longer periods of time are needed to elucidate the underlying mechanism behind this pain decrease.

In the present study the total synovitis scores on group level over 2-year period did not change, which seems to be in contrast with our previous study in which we found that patients with end-stage OA (with an indication for a knee arthroplasty) displayed more severe synovitis compared to patients who did not have an indication for a knee arthroplasty[8]. The discrepancy could be explained by the fact that a 2-year interval is too short for most patients

to progress to an end-stage disease with a significant increase in synovitis. In accordance in the present study only 4 of 61 patients progressed from baseline to an end-stage disease. Unfortunately, those patients that did progress to an end-stage were excluded because no follow-up MRI could be made.

In the present study cartilage deterioration was seen in 43.6% of patients in the tibiofemoral joint (TFJ) and in 43.6% of patients in the patellofemoral joint (PFJ) over 2 years, which is higher than described in a previous study investigating cartilage progression on MRI (27% in the TFJ, 24% PFJ)[14]. The difference in progression could be explained by the difference in study population: symptomatic patients in secondary care in present study versus a general study population in the other study. Therefore, in the present study patients were more likely to progress.

The present study has several limitations. Firstly, only 39 patients form the original 61 baseline patients were available for Gd-enhanced MRIs after 2-year follow-up. Eleven patients were not included because no CE-MRI was performed (e.g. discontinuation of MRI, contra-indications for MRI, claustrophobia), which underscores the difficulty for acquiring longitudinal data on synovitis using CE-MRI. Due to the low number of patients we could only adjust for a limited number of variables. Since our aim was to investigate synovitis change, we chose to adjust for variables that changed over time, not for baseline characteristics; baseline characteristics should not influence the results as in-patient relationships were investigated. To test this notion we ran analysis with additional adjustments for age, gender and BMI, resulting in the improvement of the effect size thus validating the found association. However, these results should be interpreted with caution and should be confirmed in larger studies. Another limitation of our study is that patients that progressed to an end-stage knee OA stage were excluded from our analysis as no follow-up MRI was available. The exclusion of these subjects could have potentially biased the study results considering that these patients often display more severe synovitis, and their inclusion could hypothetically have led to increase of mean synovitis score over time.

In conclusion our data suggest that on an individual level increase in synovitis is associated with cartilage deterioration not with pain, suggesting a role for synovitis as a target for disease-modifying treatment.

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Author contributions

Authors made substantial contributions to the following: (1a) conception and design of the study: BDL, AIF, AMZ, VSS, MK, JB; (1b) acquisition of data: BDL, AIF, EY, HK, JB, RN, MK; (1c) interpretation of data BDL, AIF, EY, HK, AMZ, VSS, RN, JB, MK; (2) drafting or critical revision of manuscript: BDL, AIF, EY, HK, AMZ, VSS, RN, JB, MK; (3) final approval of manuscript BDL, AIF, EY, HK, AMZ, VSS, RN, JB, MK.

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Conflict of interests: none

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