CHAPTER 6

ASSOCIATION OF PAIN IN KNEE OSTEOARTHRITIS WITH DISTINCT PATTERNS OF SYNOVITIS

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ABSTRACT

Objective: To determine possible patterns of synovitis on contrast-enhanced magnetic resonance imaging (CE-MRI) and its relation to pain and severity in patients with radiographic knee osteoarthritis (OA).

Methods: In total, 86 patients (mean age 62 years, 66% women, median body mass index 29 kg/m^2) with symptomatic knee OA (Kellgren/Lawrence radiographic score 3) were included. T1-weighted, gadolinium-chelate–enhanced MRI with fat suppression was used to semiquantitatively score the extent of synovitis at 11 knee sites (total score range 0–22). Self-reported pain was assessed with 3 standardized questionnaires. Principal components analysis (PCA) was used to investigate patterns (the location and severity) of synovitis. Subsequently, these patterns were assessed for associations with pain measures and radiographic severity in adjusted logistic regression models.

Results: Synovitis was observed in 86 patients and was found to be generally mild on CE-MRI (median total synovitis score 7, range 0–16). The median pain scores were 53 (range 0–96) on the visual analog scale for pain, 51.4 (range 2.8–97.2) on the Knee Injury and Osteoarthritis Outcome Score (KOOS) for pain, 35 (range 0–75) on the Intermittent and Constant Osteoarthritis Pain (ICOAP) score for constant pain, and 40.6 (range 0–87.5) on the ICOAP score for intermittent pain. PCA resulted in extraction of 3 components, explaining 53.4% of the variance. Component 1 was characterized by synovitis at 7 sites (mainly medial parapatellar involvement) and was associated with scores on the KOOS pain subscale and the ICOAP constant pain subscale. Component 2 was characterized by synovitis at 4 sites (mainly the site adjacent to the anterior cruciate ligament), but was not associated with pain measures or with radiographic severity. Component 3, characterized by synovitis at 3 sites (mainly at the loose body site), was associated with radiographic severity.

Conclusion: Different patterns of synovitis in knee OA were observed. The pattern that included several patellar sites was associated with pain, whereas other patterns showed no association, suggesting that pain perception in patients with knee OA is a localized response.

INTRODUCTION

Although one of the major outcomes of knee osteoarthritis (OA) is pain, the pathophysiologic and pain-causing mechanisms in OA remain largely unknown[1]. Studies in past years have elucidated the role of synovitis as one of the key players in pain perception, since it has been associated with pain in knee OA[2,3].

For a long time, OA was considered a noninflammatory condition. However, recently it became evident that synovial inflammation is prevalent in OA[4] and could play an important role in the pathophysiology of OA[5]. Although histologic assessment of synovitis in human synovial biopsy tissue is currently the gold standard for defining synovial inflammation, contrast-enhanced magnetic resonance imaging (CE-MRI) has proven to be a good surrogate in evaluating synovitis in patients with knee OA[6-11]. Because the anatomic distribution of synovitis on CE-MRI is patchy and heterogeneous[12], the optimal MRI scoring method should encompass a sufficient number of compartments. A method recently developed by Guermazi et al is a semiquantitative method that scores the extent of synovitis on CE-MRI at 11 different sites throughout the knee[13]and constitutes a comprehensible and practical method for assessing synovitis in the whole joint. Synovitis on CE-MRI as assessed by this scoring method compares well with synovial inflammation identified histologically in synovial biopsy tissue from patients with knee OA[9].

Only a small number of studies have investigated synovitis on CE-MRI, and even fewer studies have used a scoring system that encompasses a sufficient number of sites throughout the whole knee[12,13]. These studies have found that some sites of the knee display more synovitis than others. Whether synovitis at different sites within the knee joint occurs independently or whether distinct patterns of synovitis may form is currently unknown, since patterns of synovitis have not been investigated in an unbiased manner. Moreover, investigation of potential patterns of synovitis could contribute to the understanding of disease mechanisms in OA, as it might help to unravel both the underlying mechanisms of synovitis and the pain mechanisms involved in OA.

In the present study, we aimed to investigate whether different patterns of synovitis, as assessed by its location and extent on gadolinium-chelate–enhanced MRI of the whole knee joint, exist in patients with symptomatic primary knee OA, and if these patterns exist, whether they are associated with the extent of pain and severity of radiographic knee OA.

METHODS

Study design

This study is part of the ongoing geMstoan Study (Generation of Models, Mechanism & Markers for Stratification of Osteoarthritis Patients), an observational study in patients with established or end-stage knee OA that is aimed at finding 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

Study patients comprised individuals with symptomatic radiographic primary knee OA who were attending the rheumatology or orthopedic department of the LUMC or orthopedic department of the Diaconessenhuis Hospital (Leiden, The Netherlands) between 2008 and 2013. Symptomatic radiographic knee OA was diagnosed according to the American College of Rheumatology classification criteria for knee OA[14].

The geMstoan Study involves 2 groups of patients stratified according to a clinical end point: one group of patients with end-stage knee OA who had received a total knee arthroplasty, and another group of patients with mild to established OA who had no indication for an arthroplasty. Patients with other rheumatic diseases who had received immunosuppressive drugs or knee injections (i.e., corticosteroids) in the past 3 months were excluded. Patients with renal insufficiency (Cockcroft-Gault glomerular filtration rate <60 ml/minute) did not undergo gadolinium-chelate–enhanced MRI.

MRI acquisition

MR scanning was performed on a 3T Philips Achieva MR system (Philips Healthcare) using an 8-channel dedicated knee coil. To visualize synovitis, gadoterate meglumine (0.2 ml/kg) (Dotarem; Guerbet) was injected in the cubital vein at a rate of 2 ml/second followed by a 40-ml saline flush at a rate of 2 ml/second. CE-MRI with T1-weighted, turbo spin-echo, spectral presaturation with inversion recovery sequences and fat suppression in both the axial and sagittal planes were used for scoring the extent of synovitis. Scan parameters (for both the axial and sagittal planes) were as follows: multislice spin-echo sequence, echo train length 6 msec, time to recovery 655 msec, time to echo 20 msec, field of view 160 × 160 mm, pixel size 0.75 × 0.75 mm, slice thickness 2.5 mm, slice gap 0.8 mm, and 24 slices. Sequences were obtained between 8 and 10 minutes after injection of the contrast agent.

MRI scoring

Sagittal and axial T1-weighted, gadolinium-chelate–enhanced MRI (3T Philips Achieva MR) was used to semiquantitatively score the extent of synovitis at 11 different sites within the whole knee joint, using the scoring system of Guermazi et al[13]. Synovial thickness was measured and scored as follows: 0 = synovial thickness <2 mm, 1 = synovial thickness between 2 and 4 mm, and 2 = synovial thickness >4 mm (Figure 1). The total summed score of the 11 sites was calculated (total score range 0–22). A total MRI synovitis score of 0–4 was considered normal (no synovitis), a total score of 5–8 represented mild synovitis, a total score of 9–12 represented moderate synovitis, and a total score of >13 represented severe synovitis[13].

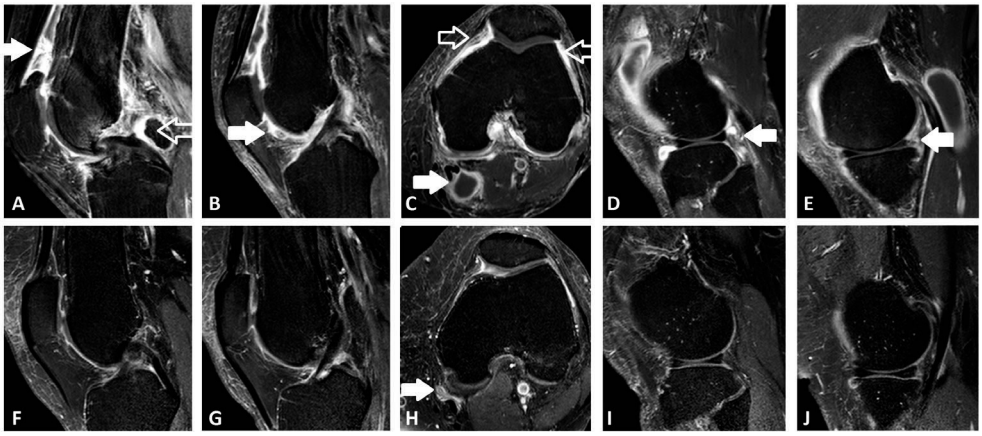

Figure 1. Scoring of synovitis on gadolinium-chelate contrast–enhanced magnetic resonance imaging (CE-MRI), using fat-suppressed T1-weighted MR images of the axial and sagittal planes. A, Sagittal CE-MRI at the level of the posterior cruciate ligament, showing synovitis and a large loose body (arrow). B, Sagittal CE-MRI at the level of the anterior cruciate ligament (ACL), showing synovitis adjacent to the ACL (#) and at the suprapatellar (white arrow), infrapatellar (*), and intercondylar (black arrow) sites. C, Axial CE-MRI, showing synovitis at both the medial (black arrow) and the lateral (white arrow) parapatellar sites and a large medial Baker's cyst with surrounding white peripheral rim indicating synovitis (*). D, Sagittal CE-MRI at the level of the tibiofibular joint, showing synovitis at the posterior horn of the lateral meniscus (arrow). E, Sagittal CE-MRI, showing synovitis at the posterior horn of the medial meniscus (arrow) and a Baker's cyst. F–J, CE-MRI of different knees at the same locations as in A–E, showing almost no synovitis. Please note the small Baker's cyst (*) in H.

Bone marrow lesions (BMLs) and effusion were scored on axial and coronal proton density–weighted images, using the Knee Osteoarthritis Scoring System in 9 compartments, as described elsewhere[15]. BMLs were defined as an ill-defined area in the subchondral bone extending from the articular surface, with a grade range from 0 to 3 as follows: 0 = absent, 1 = minimal lesion (<5 mm), 2 = moderate lesion (5–20 mm), and 3 = severe lesion (≥20 mm). For the purposes of the present analysis, BML grades were recoded into a binary variable (0 = not present, 1 = present). Effusion was scored from 0 to 3, as follows: 0 = no joint effusion,

with only a small, physiologic sliver of synovial fluid, 1 = small effusion, with 1 or 2 distended joint recesses (suprapatellar pouch, medial or lateral patellar recess, dorsal femorotibial joint space, popliteal tendon sheath, recesses surrounding the cruciate ligaments, meniscosynovial recesses), 2 = moderate effusion, with more than 2 joint recesses partially distended, 3 = massive effusion, with full, marked distention of all of the joint recesses. For the purposes of the present analysis, effusion scores were recoded into a binary variable (0 = not present, 1 = present).

All MR images were analyzed by 2 readers (BDL and AWV) by means of consensus. Both readers have >3 years of experience in scoring knee MR images (more than 1,000 MR images scored). Scoring was done after extensive learning sessions and under the supervision of an experienced musculoskeletal radiologist (JLB). During the assessment, the readers were blinded with regard to the radiographic findings and patient data. The intraclass correlation coefficient (ICC) was 0.84 (95% confidence interval [95% CI] 0.58–0.95), based on a random sample of 14 gadolinium-chelate–enhanced MR images.

Knee radiograph scoring

Radiographs of the knees of all patients (posteroanterior fixed-flexion view) were obtained. The radiographs were scored in a blinded manner by an experienced musculoskeletal radiologist (HMK) with 30 years of experience in scoring musculoskeletal radiographs. The Kellgren/Lawrence (K/L) scale for scoring radiographic damage[16] was used. The ICC was 0.99 (95% CI 0.98–0.99), based on a randomly selected sample of 36 radiographs (18 right knees and 18 left knees). Those knees assigned a K/L grade <2 were rescored in consensus between HMK and an experienced rheumatologist (MK).

Clinical data

In the geMstoan Study, patient demographic features and disease characteristics were collected from the patients via standard questionnaires. Measurement of pain was achieved using different questionnaires, each of which investigates different dimensions of pain. All questionnaires were filled in with reference to the imaged knee.

Three pain questionnaires were used. First, general self-reported pain was assessed on a visual analog scale (VAS) (scale 0–100), a one-dimensional measure of pain intensity. Participants were asked to place an “X” on a 100-mm line to represent the intensity of general pain in the reference knee. A score of 100 represents worst possible pain intensity. Second, the constant pain and intermittent pain subscales of the Intermittent and Constant Osteoarthritis Pain (ICOAP) scoring system (scale 0–100)[17] were used. Higher scores indicate worse pain experience. Third, the pain subscale of the Knee Injury and Osteoarthritis Outcome Score (KOOS) (scale 0–100)[18] was used. In contrast to all other scales, a score of 0 represents worst possible pain. Patients were asked to fill in both the KOOS and the ICOAP questionnaires to indicate the level of pain intensity experienced in the last 7 days.

Statistical analysis

For comparisons of age between groups, an independent *t*-test was used. The Mann-Whitney U test was used for comparisons of body mass index (BMI), K/L grade, MRI total synovitis score, and all pain scales. The chi-square test was used for comparisons of sex distribution and frequency of affected right knees.

Principal components analysis (PCA) was used to investigate possible patterns of synovitis. All 11 items in the synovitis scoring system of Guermazi et al[13] were subjected to PCA. Prior to performing PCA, the suitability of the data was assessed. For this purpose, the correlation matrix was inspected, which revealed correlation coefficients of ≥0.3. Furthermore, the Kaiser-Meyer-Oklin value of sampling adequacy was 0.738, which exceeded the recommended value of 0.6[19,20]. Finally, the Bartlett's test of sphericity[21] was calculated, yielding significant values ($P < 0.001$) and thereby supporting the factorability of the correlation matrix. Using eigenvalues of >1, the number of components was determined. A varimax rotation with Kaiser normalization was done to help with the interpretation of the results. In the present study, a site of synovitis was said to load significantly on a component if the factor loading was at least 0.4[22].

To investigate the association between synovitis components and pain measures and radiographic severity in patients with knee OA, regression factor scores that represented location on a factor for each patient were calculated for all components[23]. Spearman's rank correlation analysis was used to investigate the unadjusted correlations between regression factor scores and the MRI total score and clinical data. Subsequently, regression factor scores were transformed into binary variables, with 0 representing negative location on a component and 1 representing positive location on a component. A logistic regression adjusted for age, sex, and BMI, and additionally for BMLs and effusion, was used to investigate the association between components and pain and radiographic severity scores. Statistical analyses were performed using SPSS version 20.0.

RESULTS

Patient characteristics

Of the 101 patients included in the geMstoan Study (mean ± SD age 62 ± 7.5 years, 68% women, median BMI 29 kg/m^2 [range 21–49], median K/L grade 3 [range 1–4]), 87 patients had undergone gadolinium-chelate–enhanced MRI. One patient developed anti–cyclic citrullinated peptide–positive, rheumatoid factor–positive oligoarthritis after 1 year, and was therefore excluded, resulting in a total of 86 patients for analysis in the present study. These 86 patients (Table 1) did not differ significantly from the original 101 patients (results not shown) in terms of age, sex, BMI, or K/L grade. Gadolinium-chelate administration was well tolerated by all patients.

Table 1. Characteristics of the study patients (n = 86)

Age, mean ± SD years	62.3 ± 7.4
Sex, no. (%) female	57 (66)
BMI, median (range) kg/m^2	28.6 (22.0–47.8)
Right knee affected, no. (%)	45 (52)
K/L grade, median (range)	3 (1–4)
MRI total synovitis score, median (range)	7 (0–16)
ICOAP score, median (range)	
Constant pain	35 (0–75)
Intermittent pain	40.6 (0–87.5)
KOOS pain score, median (range)	51.4 (2.8–97.2)
VAS knee pain, median (range) mm	53 (0–96)

BMI = body mass index; K/L = Kellgren/Lawrence; MRI = magnetic resonance imaging; ICOAP = Intermittent and Constant Osteoarthritis Pain; KOOS = Knee Injury and Osteoarthritis Outcome Score; VAS = visual analog scale.

The patients with mild to established OA had a median K/L grade of 2 (range 1–4), and patients with end-stage disease requiring arthroplasty had a median K/L grade of 4 (range 1–4); the difference in radiographic damage scores between the groups was significant ($P < 0.001$). The percentage of female subjects was significantly lower in the end-stage OA group than in the mild to established OA group ($P = 0.007$). Moreover, as expected, all pain scale scores were significantly higher in the patients with end-stage knee OA.

Synovitis on gadolinium-chelate–enhanced MRI

The MRI synovitis scores for the affected knees of OA patients are shown in Figure 2. The median total MRI synovitis score was 7 (range 0–16) and was significantly different between the groups. The median score was 6 (range 0–14) in the mild to established OA group compared to a median score of 8 (range 1–16) in the end-stage OA group ($P = 0.005$).

Synovitis was most frequently present at the medial parapatellar site (n = 77), the site adjacent to the posterior cruciate ligament (PCL) (n = 74), the suprapatellar site (n = 65), and the lateral parameniscal site (n = 70). The site adjacent to the PCL was most frequently scored the maximal MRI synovitis score of 2 (n = 31). Loose body synovitis was found in only 6 patients. Overall, the pattern of synovitis in the mild to established OA group resembled the pattern in the end-stage OA group, although synovitis was more extensive and severe in end-stage disease (Figure 2). BMLs were seen in 76 patients (88%), whereas effusion was seen in 80 patients (93%).

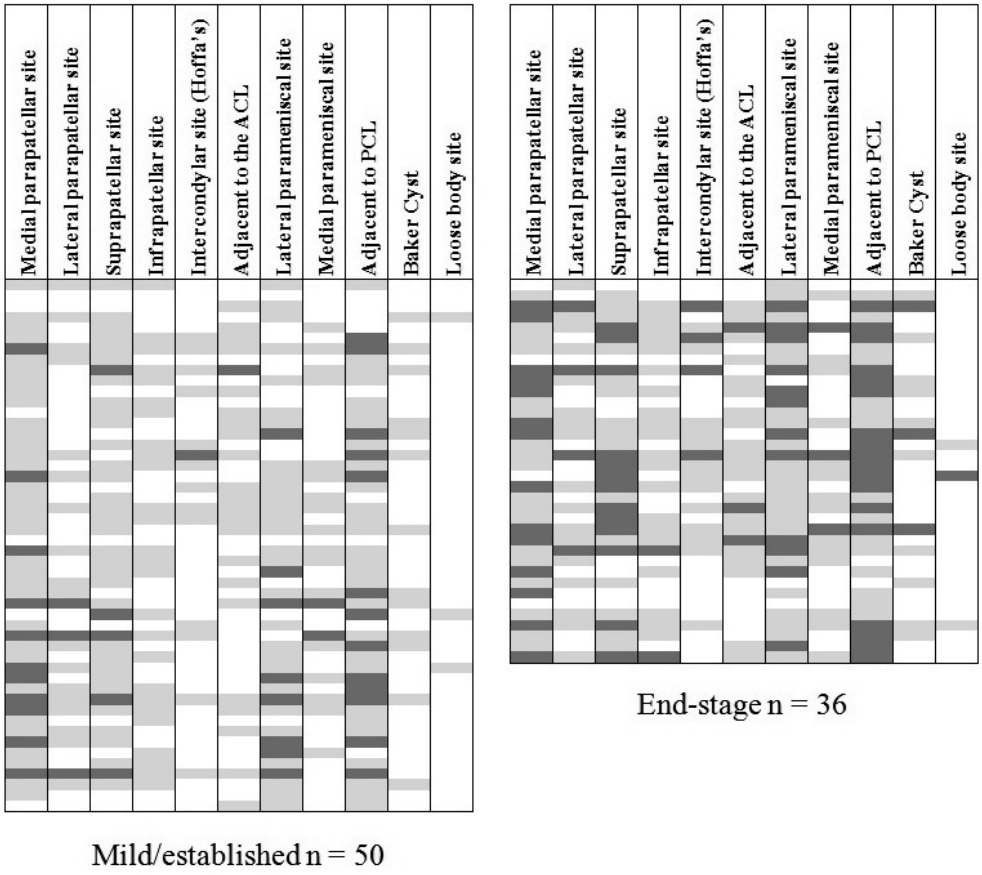

Figure 2. Total magnetic resonance imaging scores of synovitis at 11 sites of the whole knee joint in patients with mild to established knee osteoarthritis (OA) and those with end-stage knee OA requiring an arthroplasty. Each row represents 1 patient. Columns represent the 11 different sites. The score range was 0–2: 0 = white, 1 = light gray, 2 = dark gray. ACL = anterior cruciate ligament; PCL = posterior cruciate ligament.

Synovial patterns based on PCA analysis

Analysis of the MRI synovitis findings by PCA resulted in extraction of 3 components, which together explained 53.4% of the variance. After rotation, the loading factors for each anatomic site of synovitis for all 3 components were calculated (Table 2).

Component 1 was characterized by the presence of synovitis at 7 sites, with mainly medial parapatellar involvement. Component 2 was characterized by the presence of synovitis at the site adjacent to the anterior cruciate ligament (ACL) and at the medial parameniscal, intercondylar, and suprapatellar sites. Component 3 was characterized by the presence of synovitis at 3 sites (mainly at the loose body site).

Table 2. Principal components analysis with varimax rotation of a 3-component solution for 11 different knee sites on gadolinium-chelate–enhanced magnetic resonance imaging in 86 patients with symptomatic knee osteoarthritis

	Component		
	1	**2**	**3**
Anatomic site of synovitis			
Medial parapatellar	0.808		
Lateral parapatellar	0.693		
Adjacent to posterior cruciate ligament	0.538		0.506
Lateral parameniscal	0.534		
Baker's cyst	0.530		
Infrapatellar	0.488		
Adjacent to anterior cruciate ligament		0.854	
Medial parameniscal		0.622	
Intercondylar (at surface of Hoffa's fat pad)		0.533	
Loose body			0.840
Suprapatellar	0.421	0.404	0.598
% variance explained	24.4	15.6	13.4

**Only factor loadings >0.4 are displayed.*

Correlation of synovitis sites with clinical outcomes

To investigate the association between the synovitis components and the pain scores and severity of radiographic damage, regression factor scores were calculated for all 3 components. Statistically significant correlations were seen between the regression factor score for component 1 and the KOOS pain subscale score (r = −0.24; $P = 0.03$) and the ICOAP score for constant pain (r = 0.22; $P = 0.05$), but not with the other pain measures. The regression factor scores for the other 2 synovitis components and the total MRI score did not correlate with any of the pain measures. Moreover, the total MRI synovitis score did not correlate with any of the pain measures. Statistically significant correlations were observed between radiographic severity and the regression factor score for component 1 (r = 0.267; $P = 0.013$), the regression factor score for component 3 (r = 0.312; $P = 0.004$), and the total MRI score (r = 0.411; $P < 0.001$). No significant correlations between BMI and the regression factors were found.

Subsequently, the association between synovitis components and the pain and radiographic severity measures was investigated in a logistic regression model, with regression factor scores transformed into binary variables. Logistic regression adjusted for age, sex, and BMI revealed a statistically significant association between component 1 and the KOOS pain subscale score. A trend toward a statistically significant association was observed between component 1 and the ICOAP constant pain score ($P = 0.07$). Further adjustment for BMLs and effusion did not change the association between component 1 and the KOOS pain subscale score (odds ratio [OR] 0.8, 95% CI 0.6–0.998) and the ICOAP constant pain score (OR 1.3, 95% CI 1.001–1.6). Components 2 and 3 were not associated with any of the pain measures.

Furthermore, radiographic severity, as measured by the K/L grade, was significantly associated with component 3, and component 1 showed a trend toward a significant association with radiographic severity (P = 0.05) (Table 3). Sensitivity analyses restricted to only knees with a K/L grade of at least 2 decreased the association of component 1 with radiographic severity (OR 2.5, 95% CI 0.8–7.5; adjusted for BMLs and effusion, OR 1.8, 95% CI 0.6–5.8), but increased the association between component 3 and radiographic severity (OR 3.8, 95% CI 1.1–12.4; adjusted for BMLs and effusion, OR 3.4, 95% CI 1.0–11.5).

Table 3. Association of the synovitis components with pain and radiographic severity*

	Component 1	Component 2	Component 3
VAS pain[a]	1.2 (1.0–1.4)	1.1 (0.9–1.3)	1.0 (0.9–1.3)
KOOS pain[a]	0.8 (0.6–0.954)	1.0 (0.8–1.2)	0.9 (0.7–1.1)
ICOAP intermittent pain[a]	1.2 (1.0–1.5)	1.0 (0.8–1.2)	1.0 (0.8–1.2)
ICOAP constant pain[a]	1.2 (1.0–1.5)	0.9 (0.8–1.2)	1.0 (0.8–1.2)
K/L grades 3 and 4	2.7 (1.0–7.4)	0.9 (0.3–2.2)	3.2 (1.1–9.0)

** For each component (as displayed in Table 2), regression factor scores were calculated and transformed into binary variables, with 0 representing negative location and 1 representing positive location. Values are the odds ratio (95% confidence interval) adjusted for age, sex, and body mass index. VAS = visual analog scale; KOOS = Knee Injury and Osteoarthritis Outcome Score; ICOAP = Intermittent and Constant Osteoarthritis Pain (score); K/L = Kellgren/Lawrence.[a]Odds ratio shown per 10 units on pain scale.*

DISCUSSION

In the present study, we found distinct patterns of synovitis as assessed on gadolinium-chelate–enhanced MRI in patients with knee OA. Furthermore, these different patterns of synovitis seemed to be of clinical relevance, since only one pattern was associated with pain. Moreover, we demonstrated that the patterns at different stages of the disease are roughly the same, although synovitis in end-stage disease is more severe.

To our knowledge, this is the first study that has investigated patterns of synovitis on gadolinium-chelate–enhanced MRI with the use of PCA. Although synovitis in OA is known to be patchy and heterogeneous, it is not known whether the distribution of synovitis is similar in all patients or whether it differs between patients. Synovitis could differ between patients as a result of a localized response to triggers, such as a microtrauma, cartilage breakdown products, or mechanical loading. Therefore, we chose to study the 11 sites of synovitis by PCA without the inclusion of patient characteristics and without assumptions based on anatomic location.

Investigation by PCA resulted in extraction of 3 components. Component 1 explained the largest portion of the total variance and consisted of 7 sites of synovitis with mainly medial parapatellar involvement. In the present study, the results of logistic regression revealed

that only component 1 was associated with pain. Several mechanisms could underlie this observation.

Four of the 7 sites of component 1 were in the vicinity of the patella. Earlier studies on the innervation and pain sensation of the knee showed that the patellar region is richly innervated and that anterior synovial tissue in the vicinity of the patella is very sensitive to pain stimulation, which could explain the association between component 1 and pain[24,25]. The association between synovitis in the parapatellar subregion and pain is in accordance with earlier observations of an association between this region and the pain score on the Western Ontario and McMaster Universities OA index[13,26].

Although component 1 explained the largest portion of the variance and included sites that displayed the most severe synovitis (medial parapatellar site, suprapatellar site, lateral meniscal site, and site at the PCL), we do not believe that the association found could be a reflection of synovitis in the whole knee with pain. The total MRI score was not correlated with pain as assessed with the different questionnaires, thereby implicating a different mechanism underlying the association of component 1 with pain. These data suggest that each synovitis location has its location-specific properties, and further investigation is needed to unravel the underlying mechanisms.

In our study, component 2 was characterized by synovial inflammation at the ACL, medial parameniscal site, suprapatellar site, and intercondylar site. We did not find an association of this component with pain. The infrapatellar fat pad is located at the intercondylar site. Previous studies that investigated an association between synovitis at the infrapatellar fat pad on non–gadolinium-chelate–enhanced MRI and pain did not find a significant association with pain, which is in accordance with the present finding[26,27].

We found that synovitis was most frequently present at 4 sites throughout the whole knee: the site adjacent to the PCL, the medial parapatellar site, the suprapatellar site, and the lateral parameniscal site. Of these, the site adjacent to the PCL, the medial parapatellar site, and the suprapatellar site were, in a study by Roemer et al, also reported to be among the top 4 most frequent sites affected with synovitis in an American population of patients with knee OA, supporting the robustness of the present findings[12]. Remarkably, the most frequent sites of synovitis were not localized at one specific subregion of the knee, but were found throughout the whole knee, thus emphasizing that use of a system for scoring the whole knee, instead of predefined subregions, is the best way to study synovitis in patients with knee OA. This also stresses the importance of an inflammatory component of the knee joint as a whole and the purely mechanical, one-compartment origin of OA.

Loose bodies were seen in the knee joints of 7 patients. Although not frequently observed, they usually display synovitis when present, which is in accordance with other studies[12,13]. In the present study, investigation of the raw data revealed different distributions of synovitis in these 7 patients, and therefore we chose to include the loose body site in our PCA. This

resulted in a separate component, underscoring the fact that patients who have synovial inflammation at the loose body site are indeed different from other OA patients. These results, however, should be interpreted with caution and should be replicated in larger cohorts.

In the present study, we aimed to investigate different stages of OA in symptomatic patients. Therefore, we chose to divide our patients based on a hard clinical end point: those who did and those who did not receive an arthroplasty. Remarkably, a radiographic K/L grade of 4 was observed in the mild to established OA group, whereas a K/L grade of 1 was observed in the arthroplasty group. These findings underscore the discrepancy between radiographic features of OA and clinical symptoms and emphasize the fact that radiographs do not accurately define the clinical severity of OA. Sensitivity analysis in knees with a K/L grade ≥2 revealed no effect on the associations with component 1; however, the association between radiographic severity and component 3 became stronger.

The present study also has some limitations. First, only 86 patients were included in the present study, which might explain why some of the pain measures failed to reach significance in their association with component 1. Nevertheless, because the effect sizes and direction (e.g., more severe pain) were quite similar in the different pain scales, we do think our conclusions are valid. The effect sizes, however, are small, reflecting the multidimensionality of pain, which is also influenced by genetic predisposition and psychosocial factors[28-30]. Only the KOOS pain subscale score and the ICOAP constant pain score showed a statistically significant association with component 1, which confirms the notion that different pain scales measure different pain dimensions.

Furthermore, the time from gadolinium-chelate injection to acquisition of the T1-weighted images was 8–10 minutes, due to the fact that our protocol included several dynamic sequences (that are not part of the current analysis). Although some controversy exists concerning the optimal time for imaging after contrast injection [12,31,32], we believe that this could potentially have led to washout of the contrast into the cavity and might have led to increased measurements of synovial thickness. However, because the aim of the present study was to compare findings between patients, and in all patients the time after injection was comparable, the actual measurements of the synovial membrane were of lesser importance, and therefore this is less of a problem.

Finally, we adjusted our logistic regression model for age, sex, and BMI and additionally for BMLs and effusion. Although BMI was significantly correlated with all of the pain measures, it was not correlated with the components of synovitis, and therefore BMI is, by definition, not a confounder. When the models were adjusted for age and sex, both the KOOS pain subscale score and the ICOAP constant pain score were significantly associated with component 1 (results not shown), and adjustments for BMI, BMLs, and effusion did not change the effect sizes.

In conclusion, the present study confirms that the distribution of synovitis on gadolinium-chelate–enhanced MRI is patchy in patients with knee OA. This distribution is not random, because distinct patterns of synovitis on gadolinium-chelate–enhanced MRI can be identified. Furthermore, these patterns are of clinical relevance, since different patterns were associated differentially with pain. The next research step is to understand what the underlying mechanisms are for these patterns of synovitis in patients with knee OA.

Author contributions

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Kloppenburg had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. de Lange-Brokaar, Yusuf, van Osch, Stojanovic-Susulic, Bloem, Kloppenburg. **Acquisition of data.** de Lange-Brokaar, Yusuf, Visser, Kroon, Bloem, Nelissen, Kloppenburg. **Analysis and interpretation of data.** de Lange-Brokaar, Ioan-Facsinay, Zuurmond, Huizinga, Kloppenburg.

Additional disclosures

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