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Evolution of synovitis in osteoarthritic knees and its association with clinical features

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SUMMARY

Objective: To investigate the course of synovitis on contrast-enhanced magnetic resonance images (CE-MRI) in osteoarthritic knees over 2 years, and its association with pain and cartilage deterioration.
Design: Consecutive patients ($n = 39$, mean age 61 years, 79% woman, median (range) body mass index (BMI) 29 (24–48) kg/mm^2) with clinical osteoarthritis (OA) were included. Baseline and follow-up CE-MRI (3 T) were scored paired in chronological order for synovitis (semi-quantitatively at 11 sites (range 0–22)), cartilage deterioration and bone marrow lesions (BMLs) (semi-quantitatively according to Knee Osteoarthritis Scoring System (KOSS)). Changes in sum scores were calculated. Cartilage deterioration was defined as change of $\geq$2 above the smallest detectable change (SDC). Pain was assessed by standardized questionnaires. Analysis of covariance (ANCOVA) 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 (standard deviation (SD) 3.2)), although changes in individual patients were observed. Cartilage deterioration was observed in 51% of patients. Synovitis change score was lower in patients without compared to patients with cartilage deterioration, taking BML change in account (mean difference −2.1 (−4.1 to −0.1)). Change in synovitis was not associated with change in pain, whereas cartilage deterioration was associated with change in Intermittent and Constant OsteoArthritis Pain (ICOAP) constant pain in adjusted models (unstandardised coefficient (B) (95% confidence interval (CI)) 2.8 (0.4–5.3)).
Conclusions: In individual patients synovitis fluctuates during disease course. Synovitis change was not associated with change in pain. 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-

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enhanced magnetic resonance images (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 magnetic resonance imaging (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.

Materials and 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 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 3 T Philips Achieva magnetic resonance (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 150 × 150 mm, an acquisition matrix of 304×240, 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 150 × 150; 304×304 acquisition matrix. Finally CE-MRI 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/s followed by a 40-ml saline flush also at a rate of 2 ml/s. 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. Bone marrow lesions (BMLs) 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 (medial patellar site, lateral patellar site, suprapatellar site, infrapatellar site, intercondylar site (Hoffa's), site adjacent to anterior cruciate ligament (ACL), lateral parameniscal site, medial parameniscal site, site adjacent to posterior cruciate ligament (PCL), synovitis surrounding bakers cyst and synovitis surrounding loose body) 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 and 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 15% Gd-chelate enhanced MR images and was 0.93 for synovitis and 0.90 for synovitis change.

Cartilage damage and BMLs were scored according the Knee Osteoarthritis Scoring System (KOSS) score in nine 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 to 3 (0 = absent, 1 = minimal <5 mm, 2 = moderate 5–20 mm, 3 = severe ≥20 mm). 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), with 5 years of experience in scoring KOSS and synovitis following the score by Guermazi *et al.* in osteoarthritic patients. 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