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Synovitis assessed on static and dynamic contrast-enhanced magnetic resonance imaging and its association with pain in knee osteoarthritis: A cross-sectional study

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ABSTRACT

Objectives: To investigate the association between pain and peripatellar-synovitis on static and dynamic contrast-enhanced MRI in knee osteoarthritis.
Methods: In a cross-sectional setting, knee synovitis was assessed using 3-Tesla MRI and correlated with pain using the knee injury and osteoarthritis outcome score (KOOS). Synovitis was assessed in the peripatellar recesses with: (i) dynamic contrast-enhanced (DCE)-MRI, using both pharmacokinetic and heuristic models, (ii) contrast-enhanced (CE)-MRI, and (iii) non-CE-MRI. The DCE-MRI variable *IRExNvoxel* was chosen as the primary variable in the analyses.
Results: Valid data were available in 94 persons with a mean age of 65 years, a BMI of 32.3 kg/m^2 and a mean Kellgren-Lawrence grade of 2.5. *IRExNvoxel* showed a statically significant correlation with KOOS-Pain ($r = -0.34$; $p = 0.001$), as was the case with all DCE-variables but one. Correlations between static MRI-variables and KOOS-Pain ranged between $-0.21 < r < -0.29$ ($p < 0.040$). Intraclass correlation coefficients ranged between 0.90-0.99 for the heuristic and 0.66-0.93 for the pharmacokinetic DCE-MRI variables.
Conclusions: The results confirm an association between peripatellar-synovitis and pain in KOA. Overall, DCE-MRI showed stronger correlations with KOOS-Pain compared to static MRI. DCE-MRI analyses were highly reproducible and have the potential to be used to further investigate the role of inflammation and perfusion in KOA.

1. Introduction

Osteoarthritis (OA) is the most frequent form of arthritis and a leading cause of physical disability [1]. Knee OA (KOA) has traditionally been considered a degenerative disease ("*wear and tear*") of cartilage and bone [2]. It is however today generally accepted that KOA is a whole-joint disease involving all knee joint tissues [3].

Pain is the cardinal symptom of KOA [3]. Nevertheless, the basic mechanisms causing KOA pain remain unclear, but clinical, imaging, and biochemical observations indicate that low-grade intra-articular and systemic inflammation contribute to pain and disease progression [2].

Synovitis is defined as inflammation of the synovium and may manifest itself on magnetic resonance imaging (MRI) as a thickened and contrast-enhancing synovial membrane and/or indirectly as joint effusion [4]. Its role in KOA is not completely clarified but

Abbreviations: BLOKS, Boston-Leeds Osteoarthritis Knee Score; DCE-MRI, dynamic contrast-enhanced MRI; EES, extravascular, extracellular space; IRE, initial rate of enhancement; KOA, knee osteoarthritis; KOOS, knee injury and osteoarthritis outcome score; K^{trans}, volume transfer coefficient between plasma and EES; ME, maximum enhancement; MOAKS, MRI Osteoarthritis Knee Score; Nvoxel, the number of voxels with plateau or washout patterns (i.e. the highest perfused voxels); PROM, patient reported outcome measures; ROI, region of interest; TIC, time-intensity-curve; Ve, proportion of EES within a ROI/VOI; VOI, volume of interest (consisting of ≥2 ROIs).

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synovitis has been associated with pain, KOA development, severity and progression, and increased risk of knee joint replacement [3,5,6].

In contrast to conventional radiographs, MRI provides a unique visualisation of all the anatomical structures involved in KOA [3,7–11]. In the setting of KOA, MRIs are usually performed without the use of intravenous contrast even though it is generally accepted that synovitis is ideally assessed with contrast-enhanced (CE)-MRI, as only this enables the clear differentiation of synovitis from joint effusion [4]. In addition, when intravenous (IV) contrast is used, it provides the possibility to add a dynamic contrast-enhanced sequence to the MRI protocol.

Dynamic contrast-enhanced MRI (DCE-MRI) is a technique based on the sequential acquisition of rapid T1-weighted (T1w) images before and during an IV bolus infusion of Gadolinium (Gd) contrast [12]. Following the injection of the contrast agent, a temporal variation of the MRI signal intensity occurs corresponding to the underlying changes in tissue concentration of contrast agent [13]. With the appropriate software, time-intensity curves (TICs), i.e. signal intensity changes over time, can be generated and analysed quantitatively. Quantitative DCE-MRI analysis may in general be performed by two methodologies: pharmacokinetic or heuristic.

Pharmacokinetic approaches use a pre-defined model, e.g. Tofts model to characterize the TICs. Most models are based on determining the exchange of contrast agent between blood plasma and extravascular, extracellular space (EES) in each voxel using transfer rate constants such as K^{trans} (volume transfer coefficient between plasma and the EES) [13] which, in synovial samples from early arthritis patients, has been shown to be associated with von-Willebrand factor, a marker of tissue vascularity [14].

Heuristic methods are also based on a voxel-by-voxel analysis. The TICs are extracted from each voxel and assigned to different patterns of contrast uptake [15]. Furthermore, various perfusion variables can be extracted from the TICs such as the maximal enhancement (ME) and the initial rate of enhancement (IRE) [16]. In rheumatoid arthritis (RA), the IRE has shown high correlations with histological inflammation of the synovium [7]. Thus, the combination of static (conventional) and dynamic CE-MRI provides a unique ability to investigate all knee joint related structures, both in regards of morphology and perfusion. However, the relationships between the different MRI analyses of synovitis and the clinical presentation of KOA remain to be fully explored.

The aim of this study was to investigate the association between knee pain and synovitis in the peripatellar recesses assessed by static non-CE-MRI, static CE-MRI and dynamic CE-MRI in patients with KOA. We hypothesized that MRI based estimates of synovitis are correlated with pain and that synovitis assessed on DCE-MRI is stronger correlated with pain than static MRI measures of synovitis.

2. Materials and methods

2.1. Study design

In a cross-sectional setting, conventional and DCE-MRIs of osteoarthritic knees were analysed to quantify the extent of synovitis in the peripatellar recesses, using perfusion variables as surrogate markers of inflammation, and correlated with self-reported pain.

2.2. Participants

All data, except the radiographs, were obtained from the 1-year follow-up of the LIGHT-study (ClinicalTrials.gov identifier: NCT00938808), a weight loss maintenance study. Persons recruited into the LIGHT-study were former participants in a weight loss study, CAROT (ClinicalTrials.gov identifier: NCT00655941).

Eligibility criteria were as follows: age $\geq$ 50 years; baseline body mass index (BMI) $\geq$ 30 kg/m^2; clinical KOA, radiographically verified. Exclusion criteria included: lack of motivation to lose weight; former/planned knee arthroplasty; in pharmacologic treatment for obesity/planned bariatric surgery; active joint disease besides OA including significant hip OA; use of opioids. Furthermore, DCE-MRI was not performed if the patient had an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2.

In case of bilateral KOA, the most symptomatic knee was chosen as the target knee. No person was excluded due to medical conditions. The participants were asked not to change any medication during the study. The study was conducted in accordance with the Helsinki declaration of 1975, as revised in 2000, and approved by the local Ethics Committee [H-B-2009-029]. All participants gave their oral and written informed consent.

2.3. MRI protocols

MRI of the target knee was performed on a 3T Siemens Verio® system using a dedicated 16-channel send/receive knee coil. The following MRI protocol was used: coronal and axial T1w turbo spin echo (TSE) (ST 3.5 mm, FOV 150 × 150 mm, matrix resolution 0.6 × 0.5 × 3.5 mm, TE 17 ms, TR 790 ms); coronal and sagittal STIR (short tau inversion recovery) (ST 3 mm, FOV 160 × 160 mm, matrix resolution 0.7 × 0.6 × 3 mm, TI 220 ms, TE 34 ms, TR 4350 ms); sagittal 3D PDw (proton density weighted) FS (fat-suppressed) TSE SPACE (ST isotropic 0.6 mm, FOV 160 × 160 mm, matrix resolution 0.6 × 0.5 × 0. 6 mm, TE 44 ms, TR 1000 ms); sagittal 3D T1w GRE FS VIBE (ST 0.6 mm, FOV 160 × 160 mm, matrix resolution 0.6 × 0.6 × 0.6 mm, flip angle (FA) 10°, TE 5.39 ms, TR 11.6 ms). Just prior to and simultaneously with the IV injection of 0.2 ml/kg body weight Gadoteridol using a power injector (2 ml/s), a sequential axial DCE-MRI T1w GRE VIBE sequence was performed in eighteen 5 mm slices every 9 s, and with 30 repetitions covering the suprapatellar recess to the insertion of the patella tendon on the tibia using the following parameters: TE 1.86, TR 5.51, FA 15°, FOV 160 × 160, matrix resolution 192 × 138 mm (scan time 4 min, 40 s). Following this, the static 3D T1w GRE FS sequence was repeated. Total imaging time varied between 30 and 40 min.

2.4. Image analysis

A resident and PhD fellow with 4 years of experience in musculoskeletal (MSK) radiology (R.R.) performed all the MRI assessments, supervised by a senior consultant with 12 years of experience in MSK radiology (M.B.). Both were blinded to the clinical data.

2.5. DCE-MRI analyses

All DCE-MRI analyses were performed using Dynamika® Enterprise v.3.2.1 (Image Analysis Ltd., London, UK—www.imageanalysis.org.uk): after application of motion correction thus improving the signal-to-noise ratio [17], regions of interest (ROIs), were manually drawn around the synovium in the knee joint (Fig. 1). Due to difficulties in differentiating synovium from ligaments and tendons, especially in the posterior aspects of the capsule on the DCE-MRI, ROIs were only drawn around the synovium in the peripatellar recesses, i.e. the parapatellar (medial and lateral) and suprapatellar recesses (including the retropatellar space), and collapsed into one single volume of interest (VOI). The perfusion variables were subsequently extracted from the VOI.

The pharmacokinetic parameters were calculated as follows: first a point of interest for the arterial input function (AIF) was