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# The association between histological, macroscopic and magnetic resonance imaging assessed synovitis in end-stage knee osteoarthritis: a cross-sectional study

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SUMMARY

*Objectives:* To investigate the association between magnetic resonance imaging (MRI), macroscopic and histological assessments of synovitis in end-stage knee osteoarthritis (KOA).
*Methods:* Synovitis of end-stage osteoarthritic knees was assessed using non-contrast-enhanced (CE), contrast-enhanced magnetic resonance imaging (CE-MRI) and dynamic contrast-enhanced (DCE)-MRI prior to (TKR) and correlated with microscopic and macroscopic assessments of synovitis obtained intraoperatively.
Multiple bivariate correlations were used with a pre-specified threshold of 0.70 for significance. Also, multiple regression analyses with different subsets of MRI-variables as explanatory variables and the histology score as outcome variable were performed with the intention to find MRI-variables that best explain the variance in histological synovitis (i.e., highest $R^2$). A stepped approach was taken starting with basic characteristics and non-CE MRI-variables (model 1), after which CE-MRI-variables were added (model 2) with the final model also including DCE-MRI-variables (model 3).
*Results:* 39 patients (56.4% women, mean age 68 years, Kellgren–Lawrence (KL) grade 4) had complete MRI and histological data. Only the DCE-MRI variable *MExNvoxel* (surrogate of the volume and degree of synovitis) and the macroscopic score showed correlations above the pre-specified threshold for acceptance with histological inflammation. The maximum $R^2$-value obtained in Model 1 was $R^2 = 0.39$. In Model 2, where the CE-MRI-variables were added, the highest $R^2 = 0.52$. In Model 3, a four-variable model consisting of the gender, one CE-MRI and two DCE-MRI-variables yielded a $R^2 = 0.71$.
*Conclusion:* DCE-MRI is correlated with histological synovitis in end-stage KOA and the combination of CE and DCE-MRI may be a useful, non-invasive tool in characterising synovitis in KOA.


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## Introduction

Knee osteoarthritis (KOA) is the most frequent form of arthritis and has traditionally been considered a degenerative disease ("*wear and tear*") of cartilage and bone[1]. However, clinical, imaging, and biochemical observations indicate that low-grade intra-articular and systemic inflammation may contribute to pain and disease progression[1,2].

Synovitis is defined as inflammation of the synovium and is one of the hallmarks of intra-articular inflammation in KOA[1]. Synovitis has been associated with pain, disease severity, increased cartilage degradation and risk for total knee replacement (TKR)[1,3–8] and is increasingly being addressed as a treatment target in KOA[9,10]. Macroscopically, synovitis can be detected as a thickened, hyperaemic synovium[11]. Nonetheless, histological assessment from synovial biopsies remains the gold standard when assessing synovitis in KOA[12,13].

On magnetic resonance imaging (MRI), synovitis may manifest itself as a thickened and contrast-enhancing synovial membrane and/or indirectly as joint effusion[3,14]. Several studies have shown that synovitis is ideally assessed with contrast-enhanced (CE)-MRI[3,15,16]. In addition, when intravenous (IV) contrast is used, it provides the possibility to add a dynamic sequence to the MRI protocol[17,18]. Dynamic contrast-enhanced MRI (DCE-MRI) is a technique based on the sequential acquisition of rapid T1-weighted (T1w) images before and during an intravenous bolus infusion of Gadolinium contrast (Gd)[19]. Following the injection of Gd, a temporal variation of the MRI signal intensity occurs, which corresponds to the underlying changes in tissue concentration of Gd[20]. Time–intensity curves (TICs), i.e., the signal intensity increase over time, can then be generated and analysed quantitatively, either in a pharmacokinetic or heuristic approach[21].

Pharmacokinetic analyses use a pre-defined model, e.g., the extended Tofts model[22], to characterize the TICs and are based on determining transfer rate constants such as $K^{trans}$ (volume transfer constant between blood plasma and volume of extra-vascular, extra-cellular space)[22,23] which, in synovial samples from early arthritis patients, has been shown to be associated with von-Willebrand factor, a marker of tissue vascularity[24].

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[25]. Furthermore, various perfusion variables can be extracted from the TICs such as the maximal enhancement (ME) and the initial rate of enhancement (IRE)[26]. In rheumatoid arthritis (RA) the IRE has shown strong correlations with histological inflammation of the synovium[27]. Thus, the combination of conventional "static" and DCE-MRI provides a unique ability to investigate all knee joint inflammation related structures, both in regards of morphology and perfusion[3].

DCE-MRI has been used to investigate and monitor inflammatory diseases such as RA[17,26,28], but few studies have investigated the use of DCE-MRI in KOA: two recent studies showed that DCE-MRI parameters from the synovium[10,29] and Hoffa's fat pad[18] were correlated with pain and function in KOA. Yusup *et al.* recently found a statistically significant but weak correlation ($r = 0.36$) between synovitis assessed on non-CE-MRI and histological synovitis[30] and de Lange-Brokaar *et al.* found a moderate correlation ($r = 0.57$) between histological synovitis and synovitis on MRI, this time assessed on CE-MRI[31]. However, it remains unknown if and how DCE-MRI measures of synovitis relate to histological inflammation and if MRI-assessments of synovitis can explain histological synovitis in KOA.

### *Objectives & hypotheses*

The aims of this study were to: (1) describe the association between MRI, macroscopic and histological assessments of synovitis using correlation analyses, (2) explain the variance of histological synovitis with MRI-measures of synovitis using regression analyses and (3) develop an MRI-based score/algorithm to be used as a surrogate marker of synovial histological inflammation. We hypothesized that MRI-based estimates of synovitis are highly and positively correlated ($r \geq 0.70$) with histopathological findings consistent with synovitis in end-stage KOA.

## Methods

### *Study design*

In the present cross-sectional study, non-CE, CE- and DCE-MRI of end-stage osteoarthritic knees obtained prior to TKR were analysed to quantify the extent of synovitis, using perfusion variables as surrogate markers of inflammation, and correlated with microscopic and macroscopic assessments of synovitis obtained during surgery. The study was approved by the local ethical committee (N-20110031) and conducted according to the Helsinki declaration as revised in 2000. All participants gave their oral and written informed consent.

### *Study population*

The present study is based on a study investigating the association between knee synovitis and pressure pain threshold (PPT) in KOA in which the pain, biochemical and non-CE-MRI data were used[32]. In the present study, we report the static and DCE-MRI data in addition to microscopic and macroscopic data—all of which have not been presented before.

Participants were recruited from the Department of Orthopaedic Surgery, Aalborg University Hospital, Denmark, upon referral to TKR. Eligibility criteria were as follows: symptomatic, primary KOA according to the American College of Rheumatology criteria, radiographically verified[33]. In case of bilateral KOA, the knee scheduled for TKR was defined as the target knee. Subjects were excluded if any of the following criteria was present: pregnancy/planned pregnancy; other local (e.g., nerve root entrapment) or generalised pain conditions (e.g., fibromyalgia); any sensory dysfunctions; other significant musculoskeletal (MSK) disorders (e.g., hip OA); mental impairment or insufficient Danish skills precluding an informed consent; contraindications for MRI. Furthermore, (D)CE-MRI was not performed if the patient had an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 $m^2$.

### *MRI protocol*

MRI of the target knee was performed on a Philips Intera® 1.5 T system. The subjects were scanned in the supine position using a dedicated knee coil. The following MRI-sequences were performed: sagittal T1w turbo spin echo (TSE); sagittal proton density weighted (PDw) TSE; sagittal/axial/coronal PDw SPIR. Just prior to and simultaneously with the IV injection of 0.1 ml/kg body weight Gadolinium contrast (Gadobutrol) using a power injector (2 ml/s), a sequential sagittal DCE-MRI T1w sequence was performed in 23 slices every 5 s and with 40 repetitions (matrix 352 × 352, field of view (FOV) 180 mm, TE 4.6 ms, TR 8.3 ms, ST 8 mm, flip angle 12°). Following this, the static sagittal T1w TSE sequence was repeated. Total scan time varied between 20 and 30 min. The protocol can be found in details in Appendix 1.

### *Image analysis*

A resident and PhD fellow in MSK radiology (RR) performed all MRI assessments, supervised by a senior consultant in MSK