Assessing synovitis with conventional static and dynamic contrast-enhanced magnetic resonance imaging in knee osteoarthritis.

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2. Riis RG, Gudbergsen H, Henriksen M, Ballegaard C, Bandak E, Röttger D, Bliddal H et al. Synovitis assessed on static and dynamic contrast-enhanced magnetic resonance imaging and its association with pain in knee osteoarthritis: a cross-sectional study. Eur J Radiol. 2016 Jun;85(6):1099-1108. doi: 10.1016/j.ejrad.2016.03.017.
3. Riis RG, Henriksen M, Klokker L, Bartholdy C, Ellegaard K, Bandak E et al.The effects of intra-articular glucocorticoids and exercise on pain and synovitis assessed on static and dynamic contrast-enhanced magnetic resonance in knee osteoarthritis: exploratory outcomes from a randomized controlled trial. Osteoarthritis Cartilage. 2017 Apr;25(4): 481-491. doi: 0.1016/j.joca.2016.10.009

1. Background

Osteoarthritis (OA) in its various forms is the most frequent form of arthritis and is the most common cause of physical disability in the elderly population[1]. It is estimated that OA affects 4.5% of the adult population in Denmark[2] with a global prevalence of 4%[3] and OA is the 13th leading cause of years lived with disability (YLD), the leading cause being low back pain[4].

The knee is the joint most commonly affected by OA, followed by the hip joint and the joints of the wrist and hand. A recent study found that 15% of persons age 56 to 84 years had KOA[5] and the prevalence of KOA is expected to escalate with an increasing elderly and obese population[2, 6, 7] imposing substantial socioeconomic costs from treatment and productivity losses[8, 9].

1.1. Knee osteoarthritis—causes and risk factors

Osteoarthritis may be regarded as "*the result of excessive mechanical stress in a susceptible joint*"[10] resulting in pain, cartilage loss and progressive joint failure[11]. Several risk factors for the development and progression of KOA have been identified, but the exact cause(s) and aetiopathogenesis are far from being completely understood[12, 13].

Obesity is the single most important risk factor for the development of severe KOA[10, 14] and it is estimated that obesity and altered joint mechanics are the two modifiable risk factors that account for the majority of disease development and progression[10, 14, 15]. A recent systematic review and meta-analysis found that, in 25% of persons over 50 years, new onset of knee pain was related to being overweight/obese; in comparison only 5% of the cases related to previous injury[13].

The mechanisms in which obesity influences KOA-development and KOA-progression are complex and not only due to increased joint load but probably also secondary to low-grade inflammation and metabolic factors[16]. Table 1 lists known risk factors for the development and/or progression of KOA[10, 13, 17].

1.2. Inflammation in KOA

For several decades, knee osteoarthritis (KOA) was primarily considered a degenerative disease ("*wear and tear*") resulting

Table 1. Risk factors for KOA

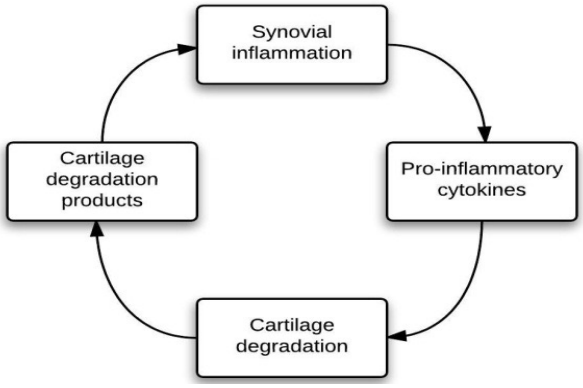
	Non-modifiable	Modifiable (target for intervention)
Female gender	X	
Age	X	
Heredity	X	
Ethnicity	X	
Previous knee injury	X	
Life-style factors		
Overweight/ Obesity		X
Sedentary lifestyle		X
Metabolic syndrome		X
Knee-related structural factors		
Biomechanical		
Malalignment (valgus/varus)		X
Adduction moment		X
Muscle strength		X
Inflammatory		
Synovitis		X
Effusion		X
Bone marrow lesions		X

in cartilage loss, the hallmark of OA[16]. It is however now generally accepted that other than mechanical factors are contributing to the development and progression of KOA, in other words KOA is a whole joint disease, involving all knee joint tissues, including the synovium, bone marrow, menisci, cartilage, ligaments, joint capsule, adipose tissues and peri-articular muscles[16-18]. Based on clinical, imaging, and biochemical observations, it has been suggested that low-grade systemic and intra-articular inflammation play an important role in the development, progression and symptomatology of KOA[16, 19].

1.2.1. Evidence of systemic inflammation in KOA

Obesity and overweight are risk factors for the development of OA not only in weight-bearing joints, e.g. the knee joint, but also in non-weight-bearing joints such as the joints of the wrist and hand[20]. Other mechanisms than biomechanical joint stress must therefore play a role in the development of OA.

Figure 1. The vicious circle of synovial inflammation and cartilage degradation.



It is now generally accepted that metabolic factors are of importance in the aetiopathogenesis of (K)OA independently of obesity at least in a subgroup of patients[19, 21-23]. Diabetes and the metabolic syndrome (MetS) are amongst others characterised by a low-grade systemic inflammation with elevated levels of inflammatory markers such as interleukin (IL)-6, C-reactive protein (CRP) and adipokines (pro-inflammatory cytokines from adipose tissues) [16]. Increased levels of IL-6 are associated with KOA-progression[24] and elevated levels of adipokines are associated with increased cartilage volume loss and risk of total knee replacement[25]. Furthermore, patients with diabetes seem to have more severe KOA than persons without metabolic changes[26], and the risk for the development and progression of KOA increases with the number of components of the metabolic syndrome present[26].

Increasing age is also a well-known risk factor for OA and some of the metabolic changes found in diabetes/MetS, i.e. increased levels of systemic inflammatory markers such as CRP, IL-6 and TNF-α (tumour necrosis factor-α) are also seen with increasing age—a phenomenon recently termed "*inflamm-ageing*"[27]. Another potential mechanism in the development of OA in the elderly may be the decrease in muscle mass and increase in fat mass resulting in both altered joint mechanics and an increase in circulating adipokines[27].

1.2.2. Evidence of local inflammation in KOA

The exact inflammatory reactions and processes that take place in the osteoarthritic joint are far from being fully understood but are thought to involve several inflammatory cells and pro-inflammatory cytokines, such as IL-1, IL-6 and TNF-α. These pro-inflammatory molecules are produced and secreted not only by immune cells such as macrophages and lymphocytes, but also by the synovial epithelium, fibroblasts, chondrocytes and adipocytes from the adjacent Hoffa's fat pad[16, 28]. The result is a local, intra-articular inflammatory environment which leads to the degradation of articular cartilage; the latter degradation products themselves amplify the synovial inflammatory reaction, thus creating a vicious circle of sustained inflammation and cartilage degradation (Figure 1). Larsson et al. showed that elevated or over time rising levels of IL-6 and TNF-α were risk factors for radiographic progression of KOA in persons with previous meniscectomy[29].

Increased knowledge about the molecular mechanisms in KOA has led to the development of potential new treatment agents, so-called DMOADs (disease-modifying OA drugs) such as IL-1- and TNF-α-inhibitors that specifically target these key molecules[30].

1.3. Inflammation and pain in KOA

Pain is the cardinal symptom of KOA[31]. Nevertheless the basic mechanisms or processes causing KOA pain remain unclear, but clinical, imaging, and biochemical observations indicate that low-grade intra-articular and systemic inflammation not only contributes to the development and progression of KOA, but also to pain and other symptoms[32, 33].

Cartilage destruction is believed to be a hallmark of knee OA. However, cartilage is avascular and aneural, wherefore the pain mechanisms in KOA are depending entirely or partially on the involvement of other structures than cartilage[33, 34].

It seems that inflammation is of importance for the development, severity and maintenance of pain in KOA[35, 36]. Stannus et al. found that an increase in pain was paralleled by an increase in high-sensitivity (hs)-CRP and TNF-α over a period of five years[37] and a systematic review and meta-analysis from 2013 found a statistically significant association between serum levels of hs-CRP and pain severity[38].

Inflammatory cytokines are known to increase responsiveness to noxious stimuli (so-called primary hyperalgesia) and lower the threshold of peripheral nociceptors causing allodynia, i.e. the painful sensation of otherwise innocuous stimuli. This can further lead to an increased responsiveness to peripheral input in the dorsal root neurons (central sensitisation) and enlargement of their receptive fields (spatial summation)[33-35, 39]. Thus, due to inflammation, a stimulus that was previously innocuous may become painful and perceived in a larger anatomical area. A recent systematic review and meta-analysis concluded that pain sensitisation is present and may be associated with symptom severity in KOA[40]and Jørgensen et al. recently found that intra-articular corticosteroid, a potent anti-inflammatory, combined with lidocaine reduced pain sensitivity in KOA[41].

Inflammatory changes in the knee joint can be detected on magnetic resonance imaging (MRI) as synovitis, including joint effusion, and signal changes in Hoffa's fat pad (HFP)[42, 43].

1.3.1. Synovitis and joint effusion

Anatomy & Physiology
The synovium is a thin membrane that lines the joint cavity of all synovial joints. It consists of cells (synoviocytes) that produce synovial fluid which acts as a lubricant.

Synovitis is defined as inflammation of the synovium and is the hallmark of intraarticular inflammation in KOA. Synovitis is a common finding in KOA and in all stages of the disease with prevalences varying from 51% to 89% in persons with or at risk of KOA[44, 45]. Synovitis is often accompanied by a joint effusion secondary to synovial activation and increased synovial permeability[46].

Histopathology
Synovitis in KOA is often more heterogeneously distributed than in rheumatoid arthritis (RA) and often confined to locations adjacent to areas with chondropathy[47]. However chondropathy is not always accompanied by adjacent synovitis which has been interpreted as if cartilage breakdown induces a local synovial reaction leading to further cartilage breakdown in a positive feed-back loop/vicious circle[48].

On a cellular level, the inflamed osteoarthritic synovium is characterised by hyperplasia of the synovial lining cell layer and cellular infiltration with, amongst others, macrophages, B- and T-lymphocytes but usually to a lower degree than in RA[9]. A recent study showed a positive correlation between the severity of synovitis and the number of mast cells in the synovium; interestingly, the prevalence of mast cells was higher in KOA than in RA of the knee[49]. By comparing synovial samples from early and late KOA, Benito et al. found increased mononuclear infiltration, overexpression of pro-inflammatory mediators, and blood vessel formation including higher levels of VEGF (vascular endothelial growth factor) in early KOA; this could indicate that synovitis is more severe in the early stages of the disease before reaching a state of chronic and low-grade inflammation[50].

Imaging
Synovitis can easily be assessed on MRI and different semi-quantitative MRI scores have been developed. On MRI, synovitis may manifest itself as a thickened and contrast-enhancing synovial membrane and/or indirectly as joint effusion. It is generally accepted that synovitis is ideally assessed on contrast-enhanced MRI due to difficulties in differentiating the synovium from an effusion[51, 52]. However, synovitis can also be visualised on ultrasound (US) and a US-scoring system has recently been proposed[53].

Association with pain in KOA
It is generally accepted that synovitis, typically assessed on MRI, is associated with pain in KOA[17, 18, 54] and changes in pain seem to be paralleled by changes in MRI-measures of synovitis[55-57]. In addition, a recent study found that synovitis and effusion assessed on MRI were associated with pain sensitisation (measured as pain pressure threshold and temporal summation) in KOA[39].

Other roles in KOA
The role of synovitis in KOA is not completely clarified: besides pain, synovitis has been associated with structural disease severity and progression[17, 58-62] as well as a risk factor for total knee arthroplasty (TKA)[63]. In recent studies, synovitis, assessed on non-CE-MRI, was identified as a risk factor for the development of radiographic KOA[64-66]. Similarly, Roemer et al. found that baseline synovitis/effusion increased the risk of cartilage loss on MRI in persons at risk of KOA[67]. As a consequence of these results, synovitis is increasingly being addressed as a treatment target in both pre-KOA and established KOA.

1.3.2. Hoffa's fat pad

Anatomy & Physiology
The infrapatellar fat pad or Hoffa's fat pad (HFP) is an intracapsular yet extra-synovial adipose structure in the anterior part of the knee joint located between the patellar ligament (anteriorly) and the synovium (posteriorly)[32, 68]. The precise

function of HFP remains largely unknown, but it has been proposed to enhance synovial fluid distribution by augmenting the synovial surface area[69, 70]. It has also been suggested that HFP plays a biomechanical role in absorbing forces generated in the knee[71].

In composition, HFP resembles more visceral than subcutaneous adipose tissue, but is, in contrary to its two counterparts, not correlated to the body mass index (BMI) and will not atrophy during extreme starvation which could indicate a physiological role in knee joint homeostasis[69].

HFP is richly innervated with nociceptive fibres and has been proposed as a source of pain not only in KOA but also several other knee conditions such as anterior knee pain and knee impingement syndromes[70]. The severe pain experienced upon endoscopic palpation of the synovial surface of the HFP is thought to be a consequence of this dense distribution of nociceptive fibres—in comparison, palpation of the patellar cartilage does not provoke any pain sensation[72]. Furthermore injections with hypertonic saline into HFP induce pain[73] and gait changes similar to the ones seen in KOA[74].

Histopathology
HFP contains adipocytes, macrophages, and other immune cells capable of producing adipokines which are thought to play an important role in the inflammatory processes in KOA[23, 27, 68, 75]. However, it remains to be determined whether the signal alterations and contrast-enhancing changes seen on MRI represent inflammation of the adipose tissue itself or herniation of the adjacent inflamed synovial membrane.

Imaging
Since the mid-1990's, fluid-like signal alterations in HFP on MRI have been used as a surrogate measure of knee synovitis in KOA; however the study that led to the conclusion was based on nine patients and purely descriptive without any statistical analyses performed[76]. In recent years, the attention has been drawn to the fact that the signal alterations in HFP on non-CE-MRI are sensitive but not specific for synovitis assessed on contrast-enhanced (CE)-MRI as the reference[77, 78]. The assessment of synovitis including signal changes in HFP should therefore optimally be performed with CE-MRI[51, 70, 77]. Nonetheless, as CE-MRI is not routinely used in KOA, signal alterations in HFP on non-CE-MRI are still assessed and used as a marker of knee synovitis in the majority of KOA-studies.

Association with pain in KOA
Signal changes in HFP on MRI are associated with pain not only in KOA[18, 77, 79] but also in older adults without KOA[80]. However when looking at the size (i.e. the maximum surface area) of HFP, the results are more difficult to interpret: Han et al. found a negative association between the surface area and pain when walking and going up/down stairs, indicating a beneficial effect of a large HFP[81]. In addition, Pan et al. reported that in a cohort of 1100 elderly without KOA, a large HFP surface area at baseline was associated with less pain over 2.5 years, however only in women[71]. Teichtahl et al. found that a large HFP was a predictor of reduced pain in KOA[82]. On the other hand, Ballegaard et al. found a positive correlation between the volume of HFP and pain[79], and Cowan et al. also reported a positive association between the volume of HFP and pain, however in patients with OA of the patellofemoral joint[83]. The lack of longitudinal data assessing changes in the volume of HFP makes it difficult to determine its exact role in KOA-pain.

Other roles of HFP in KOA
As mentioned above, the size of HFP has increasingly been studied in KOA: Han et al. found a beneficial effect of a large HFP surface area on both radiographic OA-severity, cartilage defects and volume, joint space narrowing, bone marrow lesions and osteophytes[81], and two recent studies found a beneficial association between the surface area of HFP and cartilage loss[71, 82], although only in women[71]. On the other hand, signal changes in HFP (Hoffa-synovitis) have been identified as a risk factor for the development of radiographic KOA[64, 66] further indicating that the role of HFP in KOA is not fully understood.

1.4. Other sources of pain in KOA

1.4.1. Bone marrow lesions

Bone marrow lesions (BMLs) or bone marrow oedemas (BMEs) are defined as poorly marginated areas in the subchondral bone that appear hypointense on T1-weighted MR images and hyperintense on fluid sensitive sequences[84, 85]. BMLs are a common finding not only in KOA, but also in other forms of arthritides and secondary to trauma and infections[84, 86-88].

In rheumatoid arthritis (RA), BMLs have been shown to represent osteitis with inflammatory cell infiltrates[89] and are known to predict erosive progression [90]. In KOA however, the histological nature of BMLs is poorly known. The few studies investigating the association between MRI and histopathological findings have shown non-characteristic abnormalities[88, 91, 92], but these studies have several limitations, including small sample sizes and the lack of use of intravenous (IV) Gadolinium contrast.

Despite the fact that the aetiology of BMLs and their underlying pathophysiological mechanisms remain disputed, several studies have confirmed an association between BMLs and pain in KOA[17, 57, 93-95]. Together with synovitis and effusion, BMLs are the findings most consistently associated with pain in KOA.

Besides their association with pain in KOA, there is some evidence that BMLs are also associated with incidental radiographic KOA[66] and structural progression[95], i.e. joint space narrowing on radiographs[96, 97] as well as cartilage loss on MRI[98-102]. However, a recent study found that only BMLs visible on both T1w- and T2w-images but not those only visible on T2w-images were associated with cartilage loss and pain[103]. Furthermore, BMLs in the medial tibiofemoral compartment have been shown to be a risk factor for total knee arthroplasty (TKA)[95, 104] and persons with KOA or at risk of KOA with BMLs on MRI have a greater risk of TKA compared to no BMLs[63, 100, 105].

1.4.2. Menisci

The menisci are two crescent-shaped fibro-cartilaginous structures located in the medial and lateral compartment of the tibiofemoral joint. The menisci act as stabilisers, shock absorbents and transmitters of joint load and are thus of importance for knee joint function and integrity[11].

Meniscal tears are a common finding in the general population and increase with age but the majority of the tears (> 60%) are thought to be asymptomatic[106]. In KOA, meniscal tears are even more common with a prevalence of up to 91%[107].

The role of meniscal pathology (tears, maceration, extrusion) in KOA-pain is complex[18, 107-109] as it remains to be determined whether meniscal lesions cause pain themselves or act indirectly via the development of other pain-causing lesions such as synovitis and BMLs[11]. On the other hand, it is generally accepted that the menisci play an important role in both the development and progression of KOA[66, 110]. It has been shown that meniscal position and shape are altered in KOA[111] and a recent study found an increased knee joint loading after partial meniscectomy[112]. Emmanuel et al. showed that the degree (mm) of meniscal extrusion was a predictor of radiographic KOA[113] and Crema et al. found that tears in or maceration of the medial meniscus were associated with cartilage loss in the same compartment in women age 40 and above with and without KOA[114]. In addition, Englund et al. found a six-fold increase in the risk of developing radiographic KOA over a 30-month period in persons at risk of KOA, when meniscal damage (tearing, maceration, destruction) was present at baseline[110] and similar results have been published more recently[66, 104].

As the biomechanical effects following loss of meniscal function are well-established[11], altered biomechanics and joint loading could well be (part of) the explanation of the increased risk of KOA observed with the presence of meniscal pathology and following meniscectomies[11]. In addition, Chang et al. observed that cartilage loss secondary to meniscal damage is not uniformly distributed over the articular surface but often localised in the vicinity of meniscal tears[115]—this further adds to the notion that meniscal damage leads to altered joint loading and subsequent cartilage damage. However, KOA may also itself lead to meniscal damage as a consequence of for example gait changes, altered mechanical loading, malalignment etc., making the role of the menisci in KOA undoubtedly complex.

1.4.3. Non-structural causes of pain in KOA

Pain in KOA-studies is usually assessed using validated questionnaires or visual analogue scales and is thus in its nature self-reported and subjective. The perception of pain can therefore be influenced by several other factors besides a noxious stimulus. This has led to the acknowledgement that pain in KOA is not only caused by structural lesions, altered pain-pathways and -processing but also by so-called psycho-social factors. These include one's general health status, psychological well-being (anxiety, depression, negative affect, etc.), educational level, socioeconomic circumstances and social support and seem to play an important role for the development, severity and maintenance of pain in KOA[1, 18, 116, 117]. As a consequence hereof, assessment tools have been developed to cover not only the symptoms themselves but also the impact they have on an individual level[118-120]. These aspects of pain are different from person to person and very difficult to take into account in scientific studies but should nonetheless be addressed in the management of KOA patients[14]. In a recent study, Skou et al. found that self-reported low knee confidence was associated with greater pain[121]. In addition, low knee confidence has previously been shown to predict decline in knee function in persons with or at risk of KOA[122]. These results further emphasise the importance of addressing other than structural lesions in KOA.

1.5. Knee osteoarthritis—symptoms and diagnosis

Pain is the predominant symptom in KOA; however loss of joint function including reduced strength, compromised range of motion etc., may also be the reason for patients to consult their general practitioner[123]. Flares of increased pain and eventually joint swelling can occur and are thought to be inflammatory in nature. Joint stiffness is also seen but usually resolves significantly faster than in inflammatory arthritides such as RA[124]. On clinical examination, the osteoarthritic knee is often enlarged due to bony swelling, effusion or both, eventually with crepitus and restricted passive movement. The clinical diagnosis of KOA is usually confirmed by conventional radiographs. Several clinical criteria for diagnosing KOA have been proposed[125] but the American College of Rheumatology (ACR)-endorsed criteria[126] are widely used.

Table 2. The American College of Rheumatology-endorsed diagnostic criteria for KOA[126].

Clinical criteria	Clinical and radiographic criteria
Knee pain *and* ≥ 3:	Knee pain *and* osteophytes on radiographs *and* ≥ 1:
Age > 50 years *or*	Age > 50 years *or*
Stiffness < 30 minutes *or*	Stiffness < 30 minutes *or*
Crepitus *or*	Crepitus
Bony tenderness *or*	-
Bony enlargement *or*	-
No palpable warmth	-

2. Imaging in knee osteoarthritis

Imaging plays an important role in both the diagnosis of KOA as well as assessing progression, and is an important outcome in

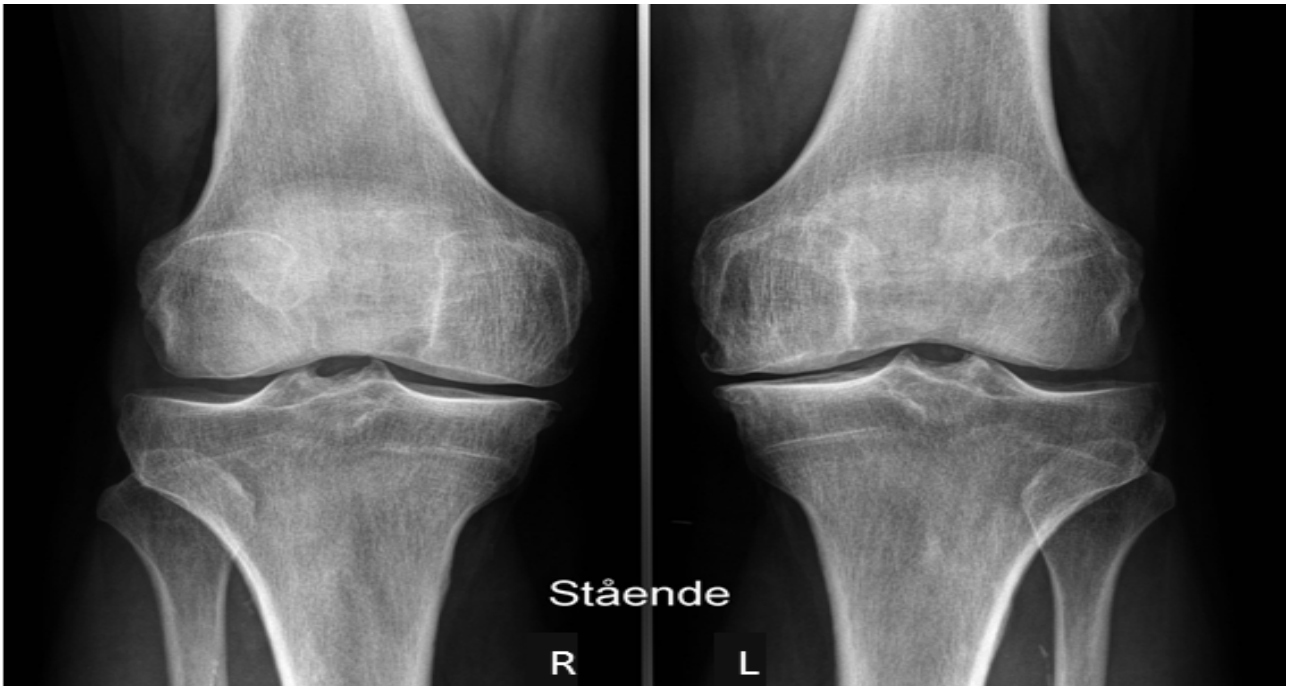


Figure 2. Standing radiography of the knees exhibiting KL-grade 3 on the left side (L) and KL-2 on the right side (R) radiographic KOA of the medial tibiofemoral compartment.

interventional studies. The different imaging modalities have contributed significantly to the understanding of KOA, however the discrepancies between imaging findings and symptoms, especially pain, warrant further development of the imaging techniques.

Conventional radiography (CR) and magnetic resonance imaging (MRI) are the modalities of choice in KOA, however ultrasound, computed tomography (CT) and positron emission tomography (PET) are also available.

2.1. Conventional radiography

In current practice, conventional radiography (CR) remain the mainstay to diagnose KOA and assess structural progression in KOA[127]. The typical osteoarthritic changes detectable on CR include joint space narrowing (JSN)/decreased joint space width (JSW), osteophytes, subchondral sclerosis and subchondral cysts. The severity of KOA on CRs is often graded using the Kellgren & Lawrence (KL) scoring system (Table 3)[128], based on especially the presence of osteophytes and joint space narrowing but other scoring systems have been proposed[129, 130]. One major reason for the wide use of CR in KOA is its high accessibility and feasibility and low costs. However, the CR scoring systems have in general shown poor associations between the radiographic severity and clinical features of KOA[127, 131]. This may be due to the fact that CR cannot capture key elements of OA pathology including inflammation and soft tissue pathology[127, 131, 132]. Nonetheless and even if structural changes on CR develop relatively slowly (over years), the US Food and Drugs Administration (FDA) still recommends radiographic JSW as an outcome for trials investigating structural modifications in KOA[133].

Table 3. The Kellgren-Lawrence classification of osteoarthritis[128].

Grade	Radiologic findings
0	No evidence of osteoarthritis (no osteophytes or joint space narrowing)
1	Possible osteophyte, doubtful joint space narrowing
2	Definite osteophyte and possible joint space narrowing
3	Moderate multiple osteophytes, definite joint space narrowing, some subchondral sclerosis, possible bone end deformity
4	Large osteophytes, marked joint space narrowing, severe subchondral sclerosis, definite bone-end deformity

2.2. Magnetic resonance imaging

The excellent soft tissue resolution of MRI enables a unique visualisation of all the anatomical structures involved in KOA, such as the synovium/synovitis, effusions, Hoffa's fat pad, bone marrow and cartilage etc.[132, 134]. As a recognition hereof, the FDA recommends the use of MRI when assessing cartilage morphology in clinical trials[135].

In general, and regardless of the different MRI-systems and -sequences, magnetic resonance imaging can be subdivided into two different techniques based on the use of intravenous gadolinium-chelated (Gd) contrast agents: non-contrast-enhanced MRI and contrast-enhanced (CE) MRI. Over the last years, a third technique, dynamic contrast-enhanced (DCE) MRI, has been increasingly used in musculo-skeletal research, primarily in the classical inflammatory arthropathies such as RA. The former two techniques are often termed conventional or static MRI as opposed to dynamic CE-MRI.

2.2.1. Conventional static non-contrast-enhanced MRI

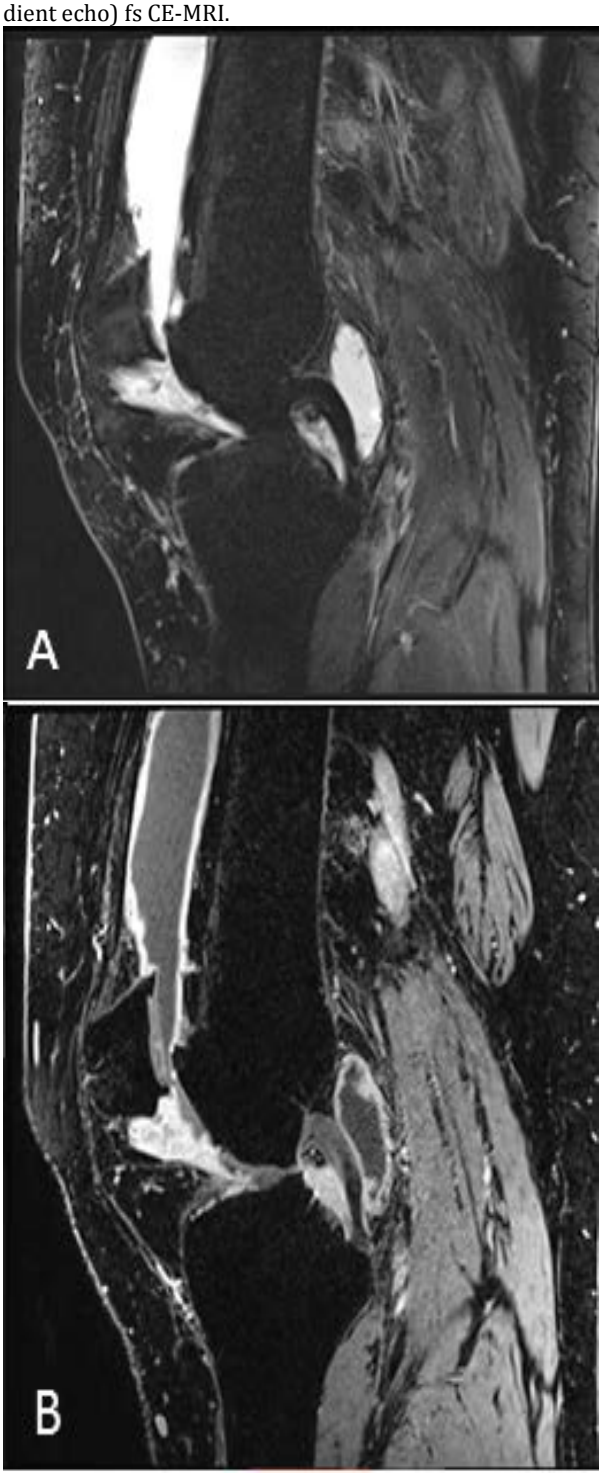
The vast majority of MRI-studies in KOA utilises non-contrast-enhanced MRI. This may be due to the increased costs and potential toxic nephrogenic side effects and allergic reactions when using intravenous Gd. However, in RA CE-MRI is recommended and usually performed, so the lack of use of Gd may also be due to the traditional idea of KOA as a non-inflammatory disease.

In an attempt to standardise the quantification of the different KOA-pathologies detectable on MRI, MRI-scoring systems that take all knee joint related structures into account have been developed; these include, amongst others, the BLOKS (Boston-Leeds OA Knee score)[42], WORMS (Whole-Organ MRI Score)[136], KOSS (Knee OA Scoring System)[137] and most recently the MOAKS (MRI in Osteoarthritis Knee Score)[43]. But as a consequence of the lack of routine use of intravenous Gd in KOA, the aforementioned MRI-scores have all been developed for non-CE-MRI despite the fact that synovitis and effusions are optimally assessed on CE-MRI.

2.2.2. Conventional static contrast-enhanced MRI

In CE-MRI, imaging is usually performed prior to and a couple of minutes after the intravenous injection of Gd. CE-MRI, consisting of for example a post-Gd T1w fat-suppressed (fs) sequence, has the advantage, compared to non-CE-MRI, to clearly depict and differentiate the contrast-enhancing synovium from joint effusions (Figure 3), which both appear hyperintense on fluid-sensitive sequences such as STIR (short tau inversion recovery) ,PDw (proton-density weighted) and T2w sequences. Not only does CE-MRI enable one to assess synovitis much more precisely, but Loeuille et al. showed that in KOA, only synovitis assessed on CE-MRI, but not on non-CE-MRI, was correlated with histological synovitis[138]. In 2011, Guermazi et al. proposed one of the few systems for the assessment of synovitis on CE-MRI in KOA[51].

Figure 3. Synovitis and joint effusion on non-CE-MRI (**A**) and CE-MRI (**B**). Note how the synovium only can be differentiated from the effusion on CE-MRI. **A**: 3D PDw fs TSE (turbo spin echo) non-CE-MRI; **B**: 3D T1w GRE (gradient echo) fs CE-MRI.



2.2.3. Dynamic contrast-enhanced MRI

In dynamic contrast-enhanced MRI (DCE-MRI), imaging is not only performed before and after but also *during* the IV injection of Gd. The DCE-MRI-sequence itself is typically based on the sequential acquisition of rapid T1-weighted (T1w) images[139]. As the distribution of Gd depends on the perfusion, DCE-MRI variables can be used as surrogate markers of perfusion.

From the DCE-MRI sequence, Gd behaviour over time can be assessed and time-intensity-curves (TICs), i.e. the change in signal intensity over time, can be generated for every single voxel[140, 141]. The generated TICs can then be analysed quantitatively, either using a heuristic or pharmacokinetic approach.

Pharmacokinetic analyses
The overall principle in pharmacokinetic analyses is to convert the signal changes secondary to the Gd-injection into pharmacokinetic parameters reflecting perfusion and permeability. This is often performed by first converting the signal changes into changes in Gd-concentration thereby creating concentration-time-curves (CTCs) and thereafter fitting these data into a pre-defined model, such as the extended Tofts model[142]. However several different pharmacokinetic models exist, some more sophisticated than others[143]. Commonly used pharmacokinetic parameters include the volume transfer constant, K^{trans}, a measure of capillary permeability and *Ve* (the proportion of extravascular, extracellular space and thus a measure of interstitial oedema). Maijer et al. recently found a positive correlation between K^{trans} and von Willebrand factor (a marker of tissue vascularity) in a mixed population of early arthritides[144].

Heuristic analyses
Heuristic DCE-MRI parameters on the other hand are typically directly extracted from the TICs without any conversion to Gd-concentrations. These heuristic DCE-MRI parameters include the *IRE* (initial rate of enhancement, i.e. the upslope on the TIC) and *ME* (maximum enhancement). As the TICs are generated as a relative increase over time in signal intensity (SI) compared to baseline values, the *IRE* is measured as SI-change(%)/second and the ME is dimensionless. Loeuille et al. found that synovial biopsies from areas with high and intermediate rates of enhancement correlated well with histological synovitis, whereas biopsies from areas with low rates of enhancement did not[46]. In addition, it seems that heuristic DCE-MRI variables are more sensitive to changes following treatment with intra-articular steroid compared to semi-quantitative CE-MRI scores in both OA[56] and RA[145].

In summary, the combination of conventional static and dynamic CE-MRI provides a unique ability to investigate all knee joint related structures both in regards of morphology and perfusion[58, 140, 146].

2.2.4. Technical considerations

For the assessment of synovitis in KOA on non-CE-MRI, T2w or PDw fat-suppressed sequences can be used[43]. On CE-MRI, synovitis is often assessed using a T1w GRE sequence with fat-suppression[51]. The optimal timing of imaging is usually two to three minutes after Gd-injection as this will ensure the visualisation of the maximal synovial enhancement without blurring of the synovium secondary to diffusion of Gd to the joint cavity[147].

DCE-MRI is typically based on T1w GRE images but the optimal parameters of the DCE-MRI sequence remain to be established. In general, a temporal resolution of 10 seconds or more (i.e. 10 seconds or less between repetitions) is recommended as especially the arterial input function and thus the pharmacokinetic parameters depend on the temporal resolution. However, improvements in temporal resolution usually necessitate a sacrifice in spatial resolution and thus a compromise in anatomical depiction.

2.2.5. Other MRI-techniques in KOA

Quantitative MRI
Based on image segmentation and analysis algorithms, the quantification of anatomical structures from MRI data sets has become possible. Especially quantitative MRI of cartilage (quantitative cartilage morphometry) has been applied in KOA studies[148], but also non-cartilage structure such as the synovium can be assessed from image segmentation[46, 55, 56]. Fully automatic quantification of ill-defined lesions/structures such as BMLs is more challenging.

Qualitative MRI
Qualitative or compositional MRI enables one to investigate the ultrastructural composition of different tissues. It has mainly been used in assessing articular cartilage and may help detect very early OA, i.e. pre-radiographic OA without any evidence of OA on conventional MRI either[149, 150].

Examples of compositional MRI-techniques for the assessment of cartilage include T2/T2*-mapping, dGEMRIC (delayed gadolinium enhanced MRI), T1rho, sodium imaging, diffusion and diffusion-tensor imaging[151].

Very simplified, T2 and T2*-imaging are based on T2/T2*-relaxation times and enable the assessment of water content, collagen fibre network and zonal variation within the articular cartilage. Damage to the cartilage matrix may lead to an increased water content which can be detected as altered relaxation times[151]. T1rho is sensitive to the slow-motion interaction between motion-restricted water molecules and the negatively charged glycosaminoglycans (GAGs) and T1rho relaxation is thought to be a marker of the content of GAGs and other macromolecules in the cartilage[151]. dGEMRIC assesses the content of GAGs based on the diffusion of negatively charged Gd-compounds (e.g. gadolinium diethylene triamine pentaacetic acid) into the cartilage. If the cartilage matrix is degraded as in KOA, Gd will diffuse into the damaged cartilage—this increased amount of Gd in the cartilage can be measured as low T1-relaxation times[152]. Sodium (^{23}Na) imaging is an MRI-technique based on the nucleus of the ^{23}Na-ion instead of the hydrogen protons of water and sodium concentration is known to be correlated with the proteoglycan concentration in cartilage[153]. Diffusion weighted imaging (DWI) is based on the (restriction of) motion of water molecules which is primarily influenced by the macromolecular environment in the extra-cellular matrix[151]. Increased diffusivity will therefore indicate structural degradation of the extra-cellular matrix. Diffusion-tensor imaging (DTI) is a DWI-technique that assesses the direction of water move-

ment and thus assesses the architecture of and collagen fibre orientation in the extra-cellular matrix. All these techniques have only been scarcely used in KOA but may have the potential to detect very early KOA.

2.3. Other imaging modalities

2.3.1. Ultrasonography

The relatively high feasibility of diagnostic high-frequency ultrasonography (US) compared to MRI has increased its use in KOA-studies. Synovitis, effusions and osteophytes can all be assessed using US[53, 154] and a validated US-score for KOA has been developed[53]. As with MRI, the addition of an IV contrast agent in possible with ultrasonography (contrast-enhanced US) and Song et al. found that CE-US is more sensitive than CE-MRI and power Doppler US in detecting synovitis in patients with painful KOA[155]. However the substantial inter- and intra-reader variability and lack of depiction of key KOA lesions such as bone marrow lesions impose a substantial limitation to the use of US in KOA.

2.3.2. Computed tomography

Despite its excellent imaging properties of bony structures, computed tomography (CT) is only to a lesser degree used in KOA-research, mainly due to the carcinogenic effects of radiation exposure. A similar technique to dGEMRIC has been developed for cone bean CT[156] but its applicability and feasibility remain to be established[157].

2.3.3. Positron emission tomography

Positron emission tomography (PET) is an extremely sensitive technique for detecting increased bone turnover/remodelling (typically using 18F-Fluoride as a tracer) and increased metabolism (using fludeoxyglucose, FDG) as seen in inflammation. One study showed that 18F-fluoride PET could detect bone abnormalities earlier than non-CE-MRI in early hip OA[158] and Mhlanga et al. found increased 18F-FDG uptake in early hand OA compared to healthy controls[159]. How these results should be interpreted from a pathophysiological and clinical point of view is still early to say.

3. Knee osteoarthritis—treatment and management

The overarching goal in the management of KOA is to improve function and alleviate pain. In addition, it is essential to address modifiable risk factors of progression.

The treatment of knee osteoarthritis can be divided into i) conservative treatment (non-pharmacological and pharmacological) and ii) surgical treatment. As no disease-modifying OA drug has been developed yet, most treatments aim at improving function and symptoms (reducing pain) and address known risk factors for the progression of the disease such as overweight and obesity.

Treatment of KOA should be multimodal and individualised: Skou et al. recently found that the combination of individualised neuromuscular training, patient education, insoles, dietary advice and prescription of pain medication (if needed) was more efficacious in improving PROMs than usual care (written and oral information and advices) 12 months later[160].

3.1. Non-pharmacological treatment

3.1.1. Exercise

Exercise, both land- and water-based, is highly recommended by both the American College of Rheumatology (ACR)[161], the European League against Rheumatism (EULAR)[162], Osteoarthritis Research Society International (OARSI)[163] and the American Academy of Orthopaedic Surgeons (AAOS)[164]. The optimal exercise programme remains to be determined[165] but may very well consist of neuromuscular training and exercises aiming at increasing strength, flexibility and aerobic capacity[166, 167]. Nonetheless, the overall benefit of exercise in decreasing pain and improving function in KOA is well-established and well-documented[166, 168].

3.1.2. Weight loss and weight loss maintenance

Overweight/obesity is one of the most important factors for the development and progression of KOA[10, 13, 15, 169]. Weight loss is therefore also highly recommended by the ACR, EULAR, OARSI and AAOS as a first-line treatment of overweight/obese persons with KOA[161-164]. As was the case with exercise, weight reduction improves physical disability[170] and pain[171, 172]. Most studies agree on a threshold of ≥ 5-10% body weight reduction in order to achieve symptomatic relief[171-173] or minimal clinical important improvement in function[174]. In addition, Gudbergsen et al. found that the symptomatic improvement following diet-induced weight loss was independent of the MRI and CR findings—in other words, weight loss is efficient regardless of radiologic disease severity[171].

In a randomised controlled weight loss trial comparing exercise, diet and the combination of exercise and diet, Messier et al. found a reduction in IL-6, a marker of systemic inflammation, in the diet and diet-exercise groups compared to the exercise alone group—this substantiates the notion of the pro-inflammatory effects of obesity and suggests an anti-inflammatory effect of dietary weight loss[172].

The role of weight loss maintenance is not fully clarified: Christensen et al. found that diet was more effective than exercise and no intervention for weight loss maintenance, i.e. the diet-group regained less weight, but no symptomatic superiority could be demonstrated[175]. On the other hand, Riddle et al. found a significant dose-response relationship between weight changes (not only loss) and pain, i.e. weight loss was followed by pain relief and weight gain was paralleled by a worsening of pain[173].

3.1.3. Self-management and patient education

Self-management programs and patient education are not only recommended as a first-line intervention in KOA[176] but also as a preventive measure (secondary prophylaxis) for persons at risk of developing KOA, e.g. persons with a history of knee injury/surgery, obese persons etc.[14, 177]. A highly-cited meta-analysis found that patient education interventions were 20% more efficient than non-steroid anti-inflammatory drugs (NSAIDs) for pain relief in OA[178].

3.1.4. Biomechanical interventions and assistive devices

There is in general a lack of agreement within the guidelines regarding the use of biomechanical assistive devices, especially braces, insoles and taping[176]. However, since adverse events are negligible, treatment with such devices may very well be attempted. The use of walking aids such as canes that unload the knee joint are in general recommended[15, 176].

3.2. Pharmacological treatment

3.2.1. Analgesics

Analgesics should be used as needed. First line analgesics include simple analgesics (paracetamol/acetaminophen) and topical analgesics (NSAID and capsaicin). A recent meta-analysis however questioned the role of paracetamol as an analgesic in knee and hip OA[179]. If pain relief is not achieved, oral NSAIDs may be added keeping the potential side effects and toxicity in mind especially in the elders. Opioids can be used as well, however the side effects may overweigh the analgesic effect[180].

3.2.2. Intraarticular corticosteroids

Intraarticular corticosteroids have been used in the management of KOA for more than five decades[181] and are still widely recommended[161, 163, 164, 176]. The therapeutic effect of intraarticular corticosteroids is unclear but is most likely related to their potent anti-inflammatory effect[182]. However the analgesic effects are short-lived (around one month) and a recent Cochrane-review has questioned the effects and routine use of intraarticular corticosteroids in KOA[183].

Other pharmacological treatments

The use of intraarticular hyaluronic acid, oral glucosamine and other nutritional supplements (marine oils, rose hip, ginger etc.) is still debated and their role in the management of KOA remains to be established.

3.3. Surgical treatment

3.3.1. Knee arthroplasty

Total knee arthroplasty (TKA) is regarded the ultimate treatment option in KOA and should be reserved for patients with advanced disease and intractable symptoms refractory to conservative therapy[15, 184].

In 2012, more than 700,000 knee joint arthroplasties were performed in the US[185](8,570 in Denmark in 2014)[186].The effects of TKA are primarily pain relief and improved function. A recent randomised controlled trial showed that TKA followed by nonsurgical treatment resulted in greater pain relief and functional improvement after 12 months than nonsurgical treatment alone but with a higher number of serious adverse events [187]. However, approximately one in five patients undergoing TKA does not achieve satisfactory results and pain persists[188-190]. The results after revision are even poorer where almost one in two will still have significant pain[191]; in addition the majority of TKA-refractory pain cases are not related to the implants themselves as pain often persists even if a problem is identified and resolved during revision[191]. These patients constitute a significant medical challenge in regards of management and treatment wherefore identification of persons at risk of a poor outcome is essential.

Pre-operative pain and function are two known predictors of poor post-TKA outcome[189, 192], in other words: the better a patient is before surgery the better they will be after it. However other factors such as area deprivation[189], low mental health and (too) high patient expectations[189, 192, 193] have also been identified as risk factors for poor outcome. Central sensitisation has also been proposed as an explanation for post-operative pain: Lundblad et al. found that a pre-operative lowered pain threshold, as a sign of central sensitisation, was a predictor of persistent pain after TKA[194]. As the number of TKAs is expected to increase[195] caution must be made in selecting potential TKA candidates and proper information and individual advice should be given[184, 196].

Unicompartmental knee arthroplasty (UKA) was developed as a less extensive alternative to TKA in patients with unicompartmental KOA, typically in the medial tibiofemoral compartment. Comparable results have been found in the few studies assessing pain after TKA and UKA[197] but it seems that TKA, in terms of prosthesis survival and revision rates, is superior to UKA but with higher perioperative complication rates[198]. Appropriate patient selection could however increase UKA prosthesis survivorship[199, 200].

3.3.2. Other surgical interventions

The role of degenerative meniscal tear surgery in KOA is not completely clarified as a substantial number of tears can be asymptomatic and the peri-operative complications may overweigh the potential protective long- term effects against structural progression. Controlled studies have also failed to demonstrate superiority of arthroscopic partial meniscectomy as compared to physiotherapy[201] in KOA or sham surgery in persons with symptoms of a degenerative medial meniscus tear but no KOA[202]. The Cochrane collaboration is currently working on a review on surgical vs. conservative interventions for treating meniscal tears[203].

Arthroscopic debridement was previously a quite common intervention in KOA but is no longer recommended[204].

4. Methodology

The following section will describe some of the recurring methods used in the three studies forming the basis of this PhD thesis. The radiographically-verified American College of Rheumatology (ACR)endorsed diagnostic criteria [126] were used for the diagnosis of KOA and inclusion of participants in all three studies. Additional details can be found in the appended original manuscripts (Appendices I-III).

4.1. Assessing synovitis on conventional static MRI

Magnetic resonance imaging was in all three studies performed with intravenous Gadolinium (Gd). This enabled us to assess synovitis and effusion on both non-contrast-enhanced and contrast-enhanced MRI. We used three validated, semi-quantitative scoring systems: the MOAKS[43], BLOKS[42] and the

whole-knee joint synovitis score as proposed by Guermazi and colleagues[44].

4.1.1. The MRI in Osteoarthritis Knee Score

The MRI in Osteoarthritis Knee Score, MOAKS, is a whole-knee score, taking all structures involved in KOA into account, and specially designed to be used with non-CE-MRI. In the MOAKS, synovitis is scored semi-quantitatively as "Hoffa-synovitis" and "effusion-synovitis": Hoffa-synovitis is defined as the extent of hyperintense signal changes in Hoffa's fat pad on midsagittal fluid-sensitive sequences (0: normal, 1: mild, 2: moderate, 3: severe). Effusion-synovitis is the combination of effusion and synovitis defined as the hyperintense signal in the suprapatellar recess on fluid sensitive sequences (0: physiological amount; 1: small—fluid continuous with the retropatellar space; 2: medium—with slight convexity of the suprapatellar recess; 3: large—evidence of capsular distension).

In Study II, where only peripatellar synovitis was assessed, we only used the effusion-synovitis score; in studies I and III, where we assessed synovitis in the entire knee, the two scores were collapsed into one single "*MOAKS-Synovitis"* score (0-6).

4.1.2. The Boston-Leeds OA Knee Score

The Boston-Leeds OA Knee Score (BLOKS) can be regarded as a predecessor of the MOAKS. One of the changes made in the MOAKS was to combine effusion and synovitis into one (the effusionsynovitis score); this was a consequence of the difficulties in differentiating synovitis from effusion on non-CE-MRI.

In the BLOKS, effusion is a separate score (0: physiological amount; 1: small—fluid continuous with the retropatellar space; 2: medium—with slight convexity of the suprapatellar recess; 3: large— evidence of capsular distension). The BLOKS-effusion assessments were in all cases performed on a CE-sequence but only the amount of intraarticular fluid was assessed. In other words, the BLOKSEffusion score represents the effusion itself whereas the MOAKS Effusion-synovitis score represents the combination of synovitis and effusion. The synovitis score of the BLOKS is identical with the MOAKS Hoffa-synovitis score and was therefore not used.

4.1.3. The whole-knee synovitis score by Guermazi et al.

In 2011, Guermazi et al. proposed a synovitis scoring system specifically developed for CE-MRI[51]. In addition, the entire synovium was assessed and not only the suprapatellar region and Hoffa's fat pad as in the MOAKS and BLOKS. The score is based on the thickness (0: < 2 mm; 1: 2-4 mm; 2: > 4 mm) of the enhancing synovium in 11 different locations in the knee (suprapatellar, infrapatellar, intercondylar, medial and lateral recess, adjacent to ACL/PCL, perimeniscal (medial/lateral), Baker cysts and around loose bodies), thereby generating a whole-knee synovitis score ("*CE-Synovitis*"), ranging from 0 to 22. Guermazi et al. proposed the following definitions of the total sum score: 0-4— normal or equivocal synovitis; 5-8—mild synovitis; 9-12—moderate synovitis and ≥ 13—severe synovitis.

As we exclusively addressed peripatellar synovitis in Study II, we only assessed and summed the peripatellar regions (suprapatellar, medial and lateral recesses) creating a score ranging from zero to six. Table 4 summarises the synovitis assessments performed on conventional static MRI in the three studies.

4.2. Assessing synovitis on dynamic contrast-enhanced MRI

4.2.1. Dynamika

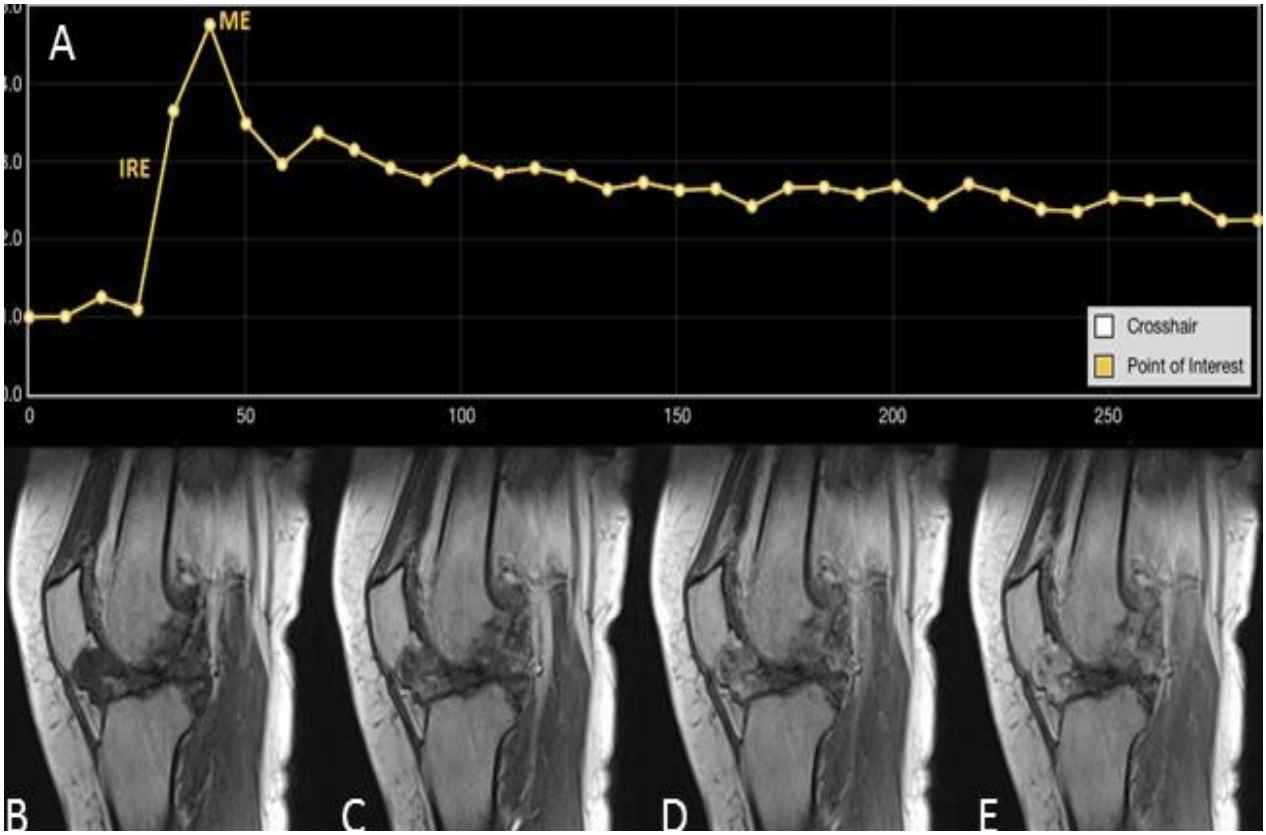
All DCE-MRI analyses in all three studies were performed with the use of Dynamika, a CE(*Conformité Européenne*) and BSi-(British Standards institution) certified software dedicated to the analysis of DCE-MRI-data. Dynamika is developed by Image Analysis Ltd., London, UK (www.imageanalysis.org.uk).

The first step, after uploading the DCE-MRI-data in Dynamika, was to perform motion correction between temporal slices: this process reduces enhancement artefacts secondary to movement between the temporal slices and increases the signal-to-noise ratio with up to 300%[205]. Secondly, a baseline level of signal intensity was determined for the calculation of heuristic DCE-MRI variables: in all three studies and in order to standardise the procedure, we chose the first three time frames as the baseline. Thirdly, regions of interest (ROIs) were manually d r

Table 4. Assessments of synovitis on conventional static MRI.

	Non-CE-MRI		CE-MRI		Comment
	MOAKS		BLOKS-Effusion	CE-Synovitis	
	Hoffa	Effusion			
Study I	-	X	X	X*	* Only peripatellar regions assessed
Study II	X	X	X	X	-
Study III	X	X	X	X	-

Figure 4. *A*: time-intensity-curve (popliteal artery) showing a steep upslope and rapid washout characteristic of areas with high perfusion. *B-E*: enhancement in the synovium and Hoffa's fat pad during the DCE-MRI sequence. *IRE*: initial rate of enhancement; *ME*: maximum enhancement.



awn around the synovium and collapsed into one single volume of interest (VOI) from which the perfusion parameters were extracted as mean values which were used in the statistical analyses. It is important to note that Dynamika calculates perfusion parameters for each single voxel within the ROI (i.e. voxel-by-voxel analysis), and that the values of the DCE-MRI variables used in the statistical analyses were calculated as means of all the voxels within the VOI (and not as means of the ROIs that constitute the VOI).

4.2.2. Heuristic DCE-MRI analyses

Heuristic DCE-MRI analysis is based on the signal intensity (SI)-changes over time. The SI-changes are calculated relatively to a baseline SI, in our studies the first three timeframes, where the Gd has not reached the knee yet. The SI-changes over time can then be plotted as time-intensity-curves (TICs) (Figure 4). From these TICs various heuristic DCE-MRI parameters can be extracted, such as the initial rate of enhancement (*IRE*, the upslope on the TIC, i.e. as the relative increase in SI measured in %/s) and the maximum enhancement (*ME*, dimensionless). In addition, the different parameters can be displayed as colour-coded parametric maps (Figure 5).

Tissues with high perfusion, such as vessels and especially arteries, are characterised by a rapid uptake of Gd (steep upslope/high IRE) and rapid washout as illustrated in Figure 4. Tissues with lower perfusion show a slower increase in Gd-uptake and will eventually not reach a plateau or washout phase. Based on this and the shape of the TIC, Dynamika assigns every voxel to one of four perfusion patterns: no enhancement (no colour), persistent (voxels that do not reach a plateau phase—blue), plateau (voxels that reach a plateau but not a washout phase—green) and washout (voxels that reach a washout phase—red) (Figure 6). In other words, plateau and washout voxels represent the highest perfused voxels. The assignment of voxels to the perfusion patterns is fully automated and based on a linear approximation of the TICs[206].

In the three studies, the number of voxels with plateau or washout patterns was assessed and summed creating the variable *Nvoxel*. As a voxel represents a volume, its size depending on the scanning parameters, we converted the number of voxels within the VOI into a volume (ml) of synovitis which was used in the analyses.

Nvoxel is a measure of the volume of the most perfused synovium, whereas the IRE and ME are surrogate measures of the degree of perfusion. We therefore chose to multiply Nvoxel by the IRE and ME, creating two composite variables, *IRExNvoxel* and *MExNvoxel*, reflecting both the volume and degree of perfusion. Nvoxel, IRExNvoxel and MExNvoxel are heuristic DCE-MRI variables that have been used previously in both RA and OA studies[79, 140, 207, 208]. We additionally multiplied the IRE by the ME as we believed these two parameters were of special interest in the characterisation of the perfusion profile of the

synovium. In summary, *Nvoxel*, *IRExNvoxel*, *MExNvoxel* and *IRExME* were the four heuristic DCE-MRI variables consistently used throughout the three studies.

Figure 5. Severe synovitis on 3D T1w GRE fs (A-B) with IRE-maps (C-D) and TICs (E) from the synovium (blue) and popliteal artery (yellow).

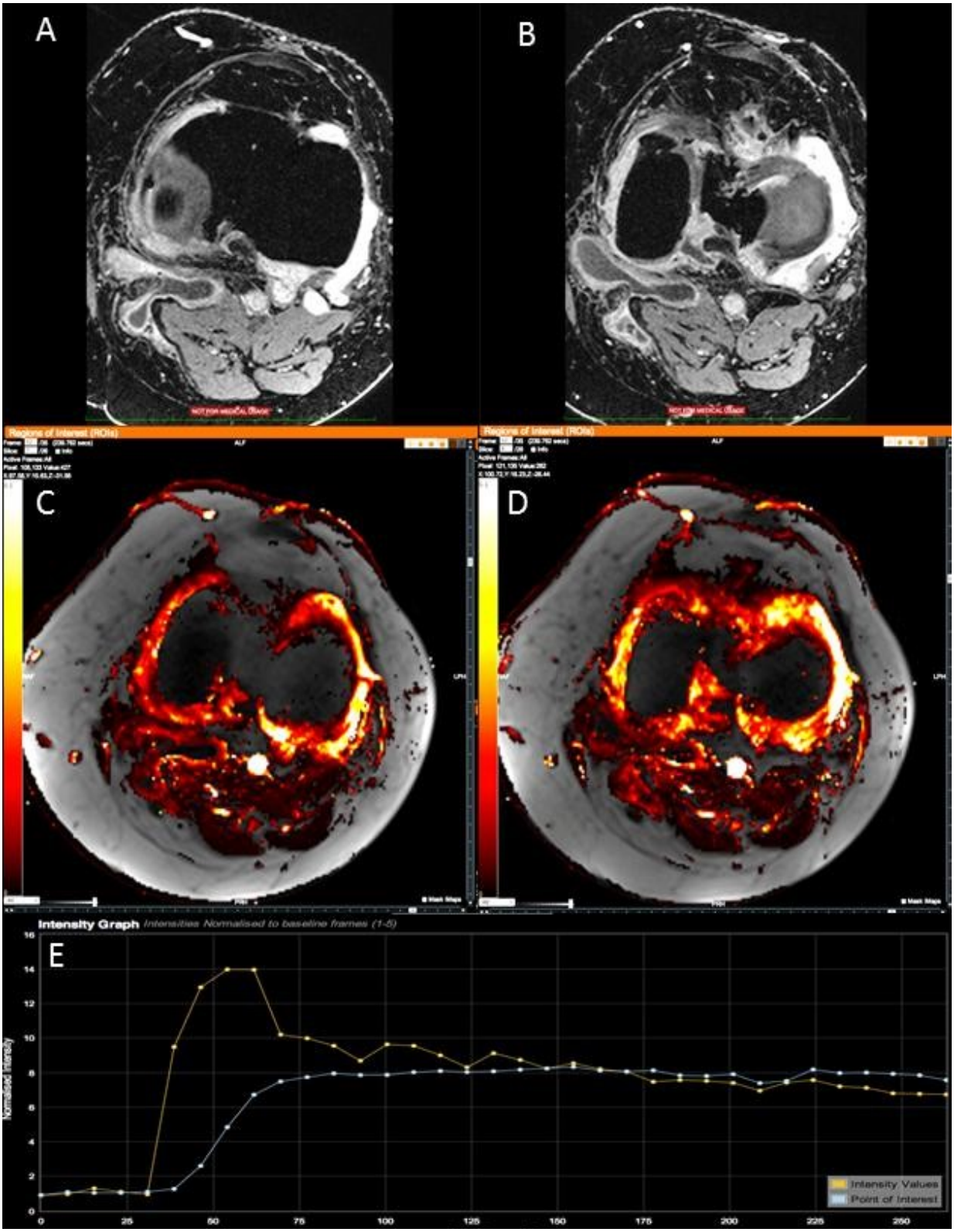
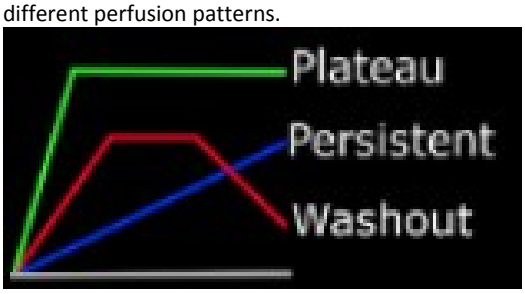


Figure 6. Schematic drawing of the time-intensity-curves of the different perfusion patterns.



4.2.3. Pharmacokinetic DCE-MRI analyses

The pharmacokinetic analyses were also performed with Dynamika and based on the extended Tofts model[142]: first a point of interest for the arterial input function (AIF) was chosen by manually finding an area within the popliteal artery with a clear arterial TIC (steep upslope and rapid washout as illustrated in Figure 4. From this arterial signal, T1-values were calculated according to:

$$Signal = \frac{M_0\left(1 - e^{TR/T1}\right)\sin(\theta)}{1 - e^{TR/T1}\cos(\theta)}$$

where:

Signal	is the recorded SPGR (spoiled gradient echo) signal intensity
M_0	is the rest magnetisation of the tissue,
TR	is the repetition time
$T1$	is the T1-value for the tissue (ms),
θ	is the flip angle for the scan

T1-values depend amongst others on the field strength of MRI-system[209]. At 3 Tesla (studies II and III), we set the T1-value of the synovium at 1280 ms and blood at 1664 ms, whereas at 1.5 Tesla (study I), the T1-values were set at respectively 1100 ms and 1428 ms[209].

The estimated changes in T1-values were then converted into changes in the concentration of the gadolinium-based contrast agent using the following equation:

$$\Delta C(t) = \Delta R1(t) r_1^{-1}$$

where:

$\Delta C(t)$	is the change in concentration in mmol/l at time t;
$\Delta R1(t)$	is the change in the rate of relaxation, R1 (i.e. 1/T1), at time t;
r_1	is the coefficient of relaxivity for the contrast medium in question

The coefficient of relaxivity was set according to Rohrer et al. based on the contrast agent and field strength[210].
As gadolinium-based contrast media are exclusively located in the extra-cellular phase, the plasmaconcentration was calculated:

$$C_P = \frac{C_B}{1 - Hct}$$

where:

C_B	is the concentration of contrast in the whole blood,
C_P	is the concentration of contrast in the plasma fraction alone, and
Hct	is the haematocrit of the patient (set at 0.42)

The pharmacokinetic parameters were subsequently estimated

$$C_t(t) = C_p(t)V_p + K^{trans}\int_0^t e^{-(\frac{K^{trans}}{V_e})(t-\tau)} C_p(\tau)d\tau$$

using the extended Tofts model[142]:

where:

$C_t(t)$	is the concentration of contrast in the tissue over time,
$C_p(t)$	is the concentration of contrast in the blood plasma over time,
$Ktrans$	is the volume transfer coefficient between the tissue and plasma
v_p	is the proportion of blood plasma in the tissue of interest
v_e	is the proportion of extravascular extracellular space in the tissue,
t	is the index of time given in minutes

As the temporal resolution was relatively high in all three studies (five to nine seconds), we used the raw data of the individual arterial TICs and AIFs; this method has been used previously[211]. Non-linear fitting of the results/data was performed on a voxel-by-voxel basis using the Levenberg-Marquardt fitting algorithm.

To summarise, the pharmacokinetic parameters used in the three studies were: K^{trans}, the volume transfer coefficient (a measure of capillary permeability) and *Ve*, the proportion of extravascular extracellular space in the tissue (a measure of

interstitial oedema). In addition, we used the *iAUGC60* (the initial area under the gadolinium curve over the first 60 seconds) in studies I and III: the conversion of change in SI into changes in Gd-concentration (Equations 2 and 3) enables the creation of a Gd-concentration graph or concentration-time-curve (CTC) illustrating the changes in Gdconcentration over time; from this CTC, the area under the curve over the first 60 seconds (iAUGC60) can be measured and used as a surrogate of perfusion and permeability (the greater a value the higher perfusion and permeability).

4.3. Microscopic and macroscopic assessments of synovitis

The following section will describe the methods used for the microscopic and macroscopic assessments of synovitis used in study I.

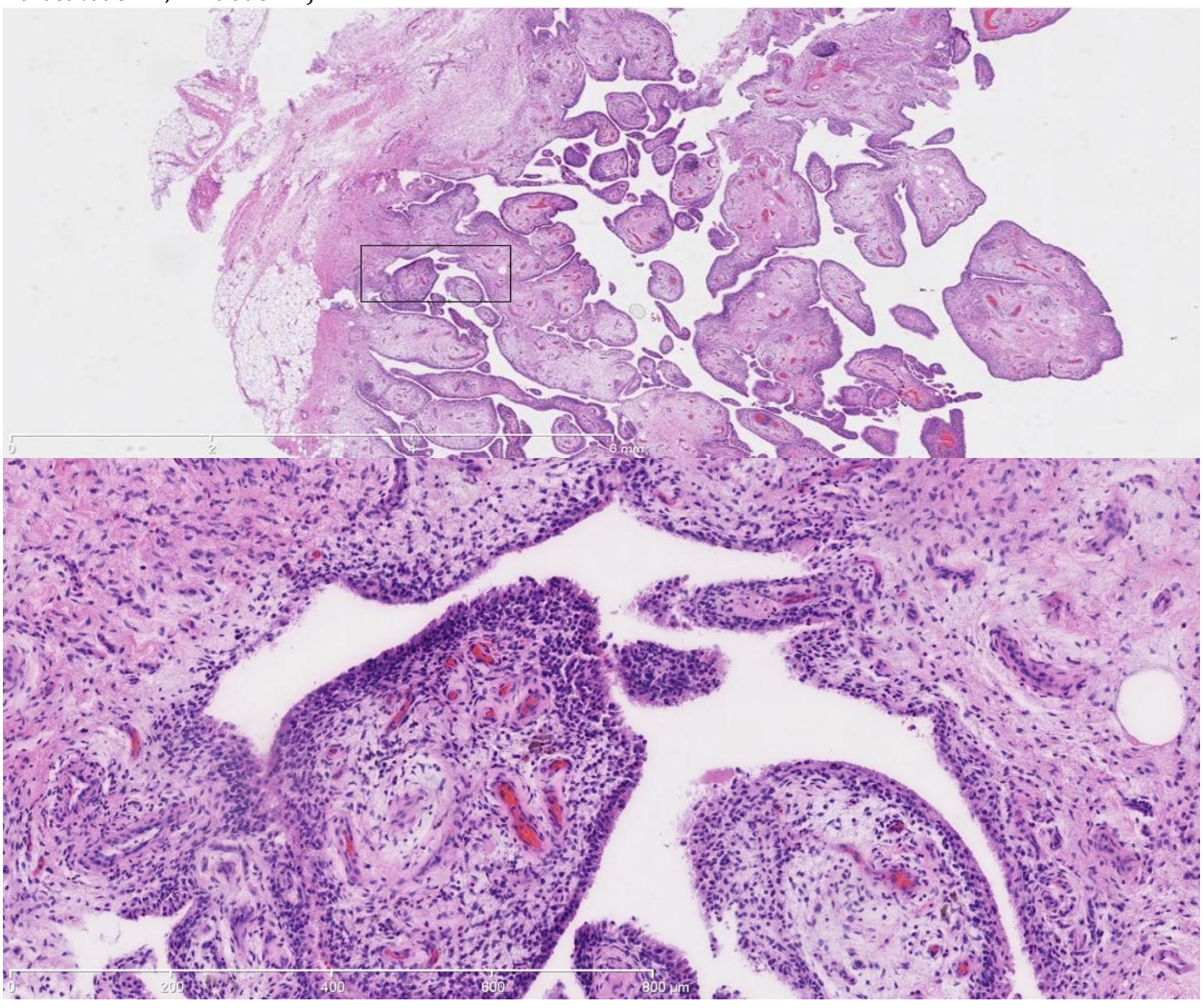
4.3.1. Microscopic assessment of synovitis

Histological assessment of synovial biopsies remains the gold standard when assessing synovitis[28, 46, 212]. However, no consensus exists on how the histological assessment of synovitis should optimally be performed and authors will often report a locally developed but not always validated scoring system[28, 46, 76, 138, 213, 214].

In 2002, Krenn et al. proposed one of the few validated scores for the assessment of chronic synovitis[212]. One of the advantages of the score is that it can be employed in conventionally (e.g.
haematoxylin-eosin) stained sections. The score is based on the semi-quantitative assessment (0-3) of three histopathological qualities characteristic of synovitis: i) hyperplasia/enlargement of the synovial lining cell layer (0: absent; 1: slight (2-3 cell layers); 2: moderate (4-5 cell layers); 3: strong (≥ 6 cell layers)), ii) inflammatory infiltration (0: absent; 1: slight (diffusely located single cells and small perivascular aggregates of lymphocytes and/or plasma cells), 2: moderate (perivascular and/or superficial lymphatic aggregates); 3: strong (lymphatic follicles with germinal centre and/or confluent subsynovial lymphatic infiltration)) and iii) activation of synovial stroma (0: absent; 1: slight (low cellularity with slight oedema and fibrosis with some fibroblasts); 2: moderate (moderate cellularity with moderate density of fibroblasts and endothelial cells); 3: strong (high cellularity with dense distribution of fibroblasts and endothelial cells, giant cells are abundant)).

In study I, where the score was used, an average grade from all the biopsies was calculated for each feature. The three averages were then summed, creating a total histology score ranging

Figure 7. Synovial excision biopsy exhibiting Krenn grade 7 synovitis (synovial lining hypertrophy: 3; stromal activation: 2; infiltration: 2).



from 0-9; this method has previously been used in KOA[215].

4.3.2. Macroscopic assessment of synovitis

As was the case with histological synovitis, a validated system for the macroscopic assessment of synovitis has been warranted[28, 46, 138, 213]. In 2009, Klint et al. published a validation-study for the macroscopic assessment of synovitis developed by their group[216]: the synovium is assessed as a whole and scored based on the extent of synovial hypertrophy, vascularity and global active synovitis (where hyperaemia is included). Each parameter is scored 0-4 and summed, creating a total macroscopic score ranging from 0-12 (0 indicating no macroscopic synovitis and 12 indicating severe macroscopic synovitis).

4.4. The Knee Injury and Osteoarthritis Outcome Score (KOOS)

The knee injury and OA outcome score (KOOS) is a self-administered patient reported outcome measure (PROM). The KOOS has been validated and compared to the WOMAC (Western Ontario and McMaster Universities OA Index)[217] and has been found to be a reliable instrument in KOAstudies218, 219.

The KOOS is constructed as a questionnaire, consisting of 42 items (questions), and assesses five different domains regarding not only pain and function but also how the knee problems influence and have an impact on the overall quality of life[120]. The five domains are: i) pain (nine items), ii) symptoms other than pain such as joint stiffness and swelling (seven items), iii) activities of daily living including ascending/descending stairs, getting in/out of cars etc. (17 items), iv) function in sports and recreation, e.g. running, jumping etc. (five items) and v) knee-related quality of life (four items). Each of the 42 items is answered by a five-point Likert scale (e.g. none-mild-moderate-severeextreme). The items that constitute each domain are subsequently scored 0-4 and summed, thereby generating a raw score for each domain. These raw scores are transformed

$$KOOS_{transformed} = 100 - \frac{KOOS_{raw} * 100}{Possible\ raw\ score}$$

to a 0-100 scale as a percentage of the total possible score:

A transformed score of 100 therefore indicates no pain/symptoms, whereas a score of 0 indicates extreme pain/symptoms.

The KOOS was applied in studies II (only KOOS-Pain) and III (all five domains) using a validated touch-screen version of the questionnaire in Danish[220]

5. Aims and hypotheses

The overarching aim of this PhD project and the three studies that comprise it was to describe and characterise synovitis in KOA using MRI and to investigate its association with PROMs and histology. This was addressed using three different approaches: first, we investigated the association between MRI-assessments of synovitis and histological synovial inflammation (study I). We then investigated the association between MRI-measures of synovitis and PROMs, first in a cross-sectional setting (study I) and subsequently in the setting of a randomised controlled trial (study III). Throughout the three studies, synovitis was assessed on conventional static non-CE-MRI, conventional static CE-MRI and dynamic contrast-enhanced MRI. As neither CE-MRI nor DCE-MRI is routinely used in KOA, we also aimed at investigating which added value the two techniques may have in KOA-research.

5.1. Study I—the histology study

Only few studies have investigated the association between synovitis, assessed on MRI, and histological synovitis in KOA[76, 214, 215]. However, the association between synovitis assessed on DCEMRI and histological synovitis has only been scarcely investigated and typically in mixed populations of both rheumatoid arthritis and osteoarthritis[144, 213]. The aim of study I was to investigate the association between histological and macroscopic synovitis and MRI-measures of synovitis using conventional static and dynamic MRI. In addition, we aimed at explaining histological synovitis with the use of both conventional static and dynamic MRI-variables.

5.2. Study II—the pain and peripatellar synovitis study

KOA has in most previous studies unfortunately been characterised by a week correlation between imaging findings and symptoms. Whether that is also the case for DCE-MRI measures of synovitis is unknown. We therefore investigated the association between pain using the KOOS and peripatellarsynovitis assessed on conventional static and dynamic MRI in a cross-sectional setting.

5.3. Study III—the corticosteroid and exercise study

Cross-sectional studies have some inbuilt limitations. We therefore chose to investigate the changes in MRI-based measures of synovitis in the setting of a randomised controlled trial with an intervention consisting of exercise and either intraarticular saline or corticosteroid. In addition, we investigated whether an improvement in pain and function (obtained via the KOOS) was paralleled by an improvement in MRI-measures of synovitis.

To summarise, the objectives of this PhD project were as follows:

- Investigate the association between MRI-measures of synovitis and histological synovitis (**Study I**).
- Explain histological synovitis using MRI-measures of synovitis **(Study I**).
- Investigate the association between synovitis assessed on MRI and pain and PROMs (**Studies II & III**).

- Investigate changes in MRI-measures of synovitis following an intervention with exercise and intraarticular saline/corticosteroid **(Study III**).
- Investigate how changes in PROMs relate to changes in MRI-measures of synovitis (**Study III**).

6. Ethical considerations

6.1. General aspects

All three studies were approved by the local ethical committee and conducted according to the Declaration of Helsinki as revised in the year 2000. Study III, was in addition conducted in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and supervised by the local Good Clinical Practice (GCP)-unit. All participants in all three studies gave their oral and written informed consent.

6.2. MRI

The use of intravenous gadolinium-containing MRI contrast-agents is in the large majority of cases safe[221]. However, side effects may occur as with any other drug. Anaphylaxis is an acute, lifethreatening systemic allergic reaction. Therefore, contrast-enhanced MRI was not performed in any person with a known or suspected allergy against Gadolinium-containing MRI contrast-agents.

As Gd-containing contrast-agents are primarily excreted renally (and to a lesser degree biliary), the administration of such contrast-agents may deteriorate an already impaired renal function. Therefore, and in accordance with the Danish Health and Medicines Authority, IV Gd-contrast was not administered to participants with an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m^2. In rare cases, Gadolinium from the contrast-agent may over time accumulate in the skin, basal ganglia and/or induce nephrogenic systemic fibrosis (in persons with impaired renal function)[222]. However the risk depends on the type of contrast-agent used. Gd-containg contrast agents are therefore classified based on the degree of Gd-release and thus risk of accumulation (low, intermediate, high risk). Only low-risk MRI contrast-agents (Gadobutrol and Gadoteridol) were used in the three studies.

6.3. Intraarticular injections

The use of intraarticular corticosteroid is safe and well-documented with few side effects, most notably septic arthritis. In order to minimise the risk of infection, intraarticular injections were conducted according to the local hygiene instructions using an aseptic injection technique. The overall risk of septic arthritis is estimated to be less than 1:10000 using this technique.

No serious adverse events secondary to any of the interventions in the three studies were recorded.

7. Methods and results

In the following section, the objectives, methods and main results of the three studies that comprise this PhD project will be described. Further details can be found in the original manuscripts appended to the thesis (Appendices I-III).

Statistical analyses were pre-defined unless otherwise stated, with a two-tailed p-value < 0.05 considered statistically significant. All analyses were performed on SAS statistical software, v. 9.3 (SAS Institute Inc.) or SPSS v. 20.0 (IBM).

7.1. Study I—associations between MRI and synovial histology

7.1.1. Objectives

The objective of this study was to investigate the association between MRI-based measures of synovitis, macroscopic and histological synovitis.

7.1.2. Methods

Design

Study I is a cross-sectional study on end-stage KOA patients, i.e. patients referred to TKA. Non-CE, CE- and dynamic CE-MRI of end-stage osteoarthritic knees obtained prior to total knee arthroplasty were analysed to quantify the extent of synovitis and correlated with microscopic and macroscopic assessments of synovitis obtained intraoperatively.

Study population

Participants were recruited from the outpatient clinic of the Department of Orthopaedic Surgery, Aalborg University Hospital, Aalborg Denmark, upon referral to TKA. Primary and radiographically verified KOA diagnosed according to the American College of Rheumatology was the main eligibility criterion whereas the main exclusion criteria included other localised or generalised pain conditions and other significant musculoskeletal (MSK) disorders (e.g. hip OA).

Image analysis

Synovitis was assessed on non-CE-MRI according to the MOAKS and on CE-MRI according to the whole-knee synovitis score proposed by Guermazi et al. In addition, effusion was scored on CE-MRI according to the BLOKS. Both heuristic and pharmacokinetic DCE-MRI parameters were used.

Microscopic assessment

In order to cover the most of the synovium, excision biopsies were taken from four standardised location within the knee cavity (anteriorly and posteriorly in the suprapatellar recess and from the medial and lateral parapatellar recesses). In addition, biopsies were taken from the area with the most severe synovitis macroscopically and the most severe synovitis on MRI. Based on these six biopsies, means of each of the three subscales (synovial hypertrophy, cellular infiltration and stromal activation) were calculated and summed creating a whole-knee microscopic synovitis score (0-9).

Macroscopic assessment
A macroscopic synovitis score was obtained by summing the three subscales of the scoring system proposed by Klint et al., i.e. synovial hypertrophy, vascularity and active synovitis, thus creating a whole-knee macroscopic score 0-12.

Statistics
First, Spearman's correlations were calculated for all included variables (patient characteristics, MRI, microscopic and macroscopic variables). In order to compensate for the issue of multiple testing, only correlations coefficients ≥ 0.70 were regarded as statistically significant. Secondly, multiple regression analyses were performed with the patient characteristics and MRI-variables as explanatory and the histology score as outcome variable. As contrast-enhanced MRI is not routinely performed in KOA, we chose to perform three multiple regression analyses with different sets of explanatory variables in order to increase the feasibility and clinical applicability:

- Model 1: patient characteristics and non-CE MRI variables
- Model 2: the aforementioned variables from model 1 and the CE-MRI variables
- Model 3: the variables from the two previous models and all DCE-MRI variables

In all three cases, multiple regression analyses were performed with the intention to find the subset of explanatory variables (MRI) that yielded the largest adjusted R^2, i.e. explain variance in the outcome variable (histology).

7.1.3. Results

39 participants (56% females, mean age 68 years, median KL grade 4) had complete MRI and histological data. Only the heuristic DCE-MRI-variable *MExNvoxel* (composite score reflecting the degree (ME) and volume of synovitis (Nvoxel) and the macroscopic score showed statistically significant correlations above the pre-specified threshold of significance of r ≥ 0.70

Table 5. Spearman's correlation matrix.

		Micro-total	Macro-total
Histology	Micro-total	1.00	
Macroscopy	Macro-total	0.72*	1.00
DCE-MRI (heuristic)	Nvoxel	0.66	0.67
	MExNvoxel	0.70*	0.72*
	IRExNvoxel	0.59	0.68
	IRExME	0.39	0.55
DCE-MRI (pharmacokinetic)	K_{trans}	0.68	0.38
	Ve	-0.12	-0.21
	iAUGC60	0.30	0.42
CE-MRI	CE-Synovitis	0.68	0.63
	BLOKS-Effusion	0.47	0.40
Non-CE-MRI	MOAKS-Synovitis	0.54	0.54

Table 6. Multiple regression analyses for the different subsets of explanatory variables (MRI) and the outcome variable (histology).

	Highest adjusted R^2	p-value
Model 1: Patient characteristics Non-CE-MRI	0.39 (SEE=1.00)	p=0.0005
Model 2: + CE-MRI	0.52 (SEE=0.86)	p<0.0001
Model 3: + DCE-MRI	0.71 (SEE=0.73)	p<0.0001

SEE: standard error of the estimate

(Table 5). In the regression analyses, adding the static CE-MRI variables (i.e. going from model 1 to model 2), increased the maximum R^2 from 39% to 52%. By further offering the DCE-MRI variables, a model consisting of the gender, one static CE-MRI and two DCE-MRI variables yielded a R^2 of 71% (Table 6).

7.2. Study II—associations between pain and peripatellar synovitis

7.2.1. Objectives

The objective was to investigate the associations between pain and peripatellar synovitis assessed on non-CE-MRI, CE-MRI and DCE-MRI in KOA.

7.2.2 Methods

Design
In a cross-sectional setting, we investigated the association between pain and peripatellar synovitis assessed on static conventional and dynamic contrast-enhanced MRI.

Study population
The study population consisted of participants in a weight loss maintenance study (ClinicalTrials.gov identifier: NCT00938808). The data used in study I originated from the one-year follow up. Inclusion criteria were as follows: age ≥ 50 years; baseline body mass index BMI ≥ 30 kg/m²; 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.

Image analysis
Peripatellar synovitis was assessed on non-CE-MRI according to the MOAKS and on CE-MRI according to Guermazi et al. In addition effusion was assessed on CE-MRI using the BLOKS. Both heuristic and pharmacokinetic DCE-MRI parameters were generated and used.

Patient reported outcome measures
Pain was assessed using the KOOS-questionnaire (0 indicating extreme pain and 100 no pain).

Statistics
First, Spearman's correlations coefficients between the MRI-variables and KOOS-Pain were calculated. This was followed by simple linear regression analysis for each of the MRI-variables (independent variable) as and KOOS-Pain (dependent variable). From these, only potentially statistically significant variables were included in the multiple regression analyses. Due to collinearity, two separate multiple regression analyses were performed, one with the conventional static MRI variables and one with the DCE-MRI variables followed by automatic reduction of the models. Lastly, intra- and inter-reader reliability was assessed using Bland-Altman plots and intra-correlation coefficients (ICCs).

7.2.3. Results

94 patients had complete MRI and KOOS-Pain data (82% female, mean age 65 years and BMI 32 kg/m²). Overall, the majority of MRI-variables (eight out of nine) showed statistically

Table 7. Spearman's correlations between KOOS-Pain and MRI variables.

	DCE-MRI (heuristic)			DCE-MRI (pharmacokinetic)			CE-MRI		Non-CE-MRI
	Nvoxel	MExNvoxel	IRExNvoxel	IRExME	K_{trans}	Ve	CE-Peripatellar	BLOKS-Effusion	MOAKS-Effusion
KOOS-Pain	-.27**	-.32**	-.34**	-.37**	-.35**	.04	-.22*	-.21*	-.29**

**p<0.01; *p<0.05

significant correlations with KOOS-Pain, with a tendency of the DCE-MRI variables being stronger correlated than the conventional static MRI-variables (Table 7). Of these latter, the MOAKS-Effusion score (combination of synovitis and effusion in the suprapatellar recess on non-CE-MRI) showed the strongest correlation with KOOS-Pain. MOAKS-Effusion also turned out to be the strongest explanatory variable of KOOS-Pain in the multiple regression analysis with the conventional static MRI-variables (Table 8). MExNvoxel (composite score reflecting the volume of synovitis (Nvoxel) and degree of perfusion (ME)) was the strongest explanatory DCE-MRI variable (Table 9). ICCs ranged between 0.66-0.93 for the pharmacokinetic parameters, between 0.90-0.99 for the heuristic DCE-MRI variables and 0.88-0.98 for the conventional static MRI variables. The Bland-Altman plots did not indicate any systematic errors.

7.3. Study III—changes in synovitis, pain and symptoms following exercise and intraarticular corticosteroids

7.3.1. Objectives

The objectives of study III were to: i) describe and compare the changes in MRI-assessments of synovitis following an exercise program preceded by an intraarticular injection of either corticosteroid or isotonic saline and ii) investigate if any of the changes in PROMs were associated with changes in MRI-measures of synovitis.

Table 8. Regression analyses—static conventional MRI vs. KOOS-pain.

Explanatory variables	Simple linear regression model	Reduced multiple regression model	Adjusted for age, sex, BMI
CE-Peripatellar	-2.775 p=0.012 (-4.925; -0.625)	-	-
BLOKS-Effusion	-5.403 p= 0.020 (-9.929; -0.877)	-	-
MOAKS-Effusion	-6.333 p=0.003 (-10.473; -2.194)	-6.333 p=0.003 (-10.473; -2.194)	-5.972 p=0.007 (-10.263; -1.681)

Table 9. Regression analyses—DCE-MRI vs. KOOS-pain.

Explanatory variables	Simple linear regression model	Reduced multiple regression model	Adjusted for age, sex, BMI
Nvoxel	-0.348 p=0.044 (-0.687; -0.009)	-	-
IRExNvoxel	-10.877 p=0.089 (-23.463; 1.709)	-	-
MExNvoxel	-0.133 p<0.0001 (-0.245; -0.020)	-0.133 p<0.0001 (-0.245; -0.020)	-0.133 p<0.0001 (-0.245; -0.020)
IRExME	-301.953 p<0.0001 (-444.682; -159.225)	-	-
K^{trans}	-70.713 p=0.037 (-137.052; -4.375)	-	-
Ve	-18.962 p=0.465 (-70.338; 32.415)	-	-

7.3.2. Methods

Design
Study III is based on a participant-, care provider-, outcome assessor blind, two-arm, parallel-group, randomised and placebo-controlled trial investigating the effects of intraarticular corticosteroids compared to intraarticular saline given two weeks prior to an exercise programme. Synovitis was assessed with MRI at baseline, after the termination of the exercise programme (week 14—primary endpoint) and 12 weeks later (week 26—follow-up). Participants were randomized equally (1:1) to receive an intra-articular injection of either corticosteroid or placebo at baseline.

Study population
Participants were recruited from the osteoarthritis outpatient clinic, Copenhagen University Hospital,

Bispebjerg-Frederiksberg, Denmark with the following inclusion criteria: age ≥ 40 years, radiographically verified diagnosis of tibiofemoral OA (ACR criteria), clinical signs of localised knee inflammation, knee pain during walking (> 4 on a 0-10 point scale), and a BMI ≤ 35 kg/m^2. Exclusion criteria included: corticosteroid injections or participation in exercise therapy within 3 months, current/recent (within 4 weeks) use of oral corticosteroids, contraindications to corticosteroid injections, conditions precluding participation in exercise, inflammatory arthritis, history of knee arthroplasty or osteotomy, generalised pain syndromes (e.g. fibromyalgia) and local nerve root compression syndromes.

Image analysis
Synovitis was assessed on non-CE-MRI according to the MOAKS and on CE-MRI according to Guermazi et al. In addition, effusion was assessed on CE-MRI using the BLOKS. Both heuristic and pharmacokinetic DCE-MRI parameters were used.

Patient reported outcome measures
PROMs were assessed using the five KOOS domains (pain, quality of life, activities in daily living, function in sports and recreation and symptoms).

Statistics
The statistical analyses were carried out on a modified intention-to-treat population defined as assessable MRI-data at baseline. Missing data were replaced using multiple imputations using age, gender, BMI, group allocation (masked) and baseline scores as predictors.

The primary analysis was to compare the differences in the mean changes in the MRI-assessments of synovitis (both static and dynamic) between the two groups (corticosteroid vs. placebo) from baseline to week 14 (primary endpoint) and 26. We used repeated measures mixed linear models, including participants as a random effect, with fixed factors for group (2 levels) and week (2 levels (weeks 14 and 26)) and the corresponding interactions, adjusted for baseline values. To assess the association between changes in synovitis on MRI and PROMs, linear regression was performed with the PROMs as outcome and MRI-assessments of synovitis as predictor variables (aim no. 2). For all MRIvariables, simple linear regression was first performed. From these analyses only potentially significant MRI-variables (defined as p<0.10) were included in the multiple regression analyses followed by adjustment for age, gender, BMI and allocation group. Intra-class correlation coefficients (ICCs) were calculated for all MRI-variables.

7.3.3. Results

91 of the 100 randomised participants had complete DCE-MRI data at baseline (46 in the placebo group and 45 in the corticosteroid group) and constituted the modified intention-to-treat population. Of these, 78 participants complied with the first follow-up (week 14) and 63 completed the study, i.e. DCE-MRI data at baseline, weeks 14 and 26 (Figure 8).

The placebo group was on average older (mean difference: 5.1 years; 95% CI: 1.3-8.8) and had a higher BLOKS-Effusion score (mean difference: 0.31; 95% CI: 0.03-0.59) and KL-grade (mean difference: 0.4; 95% CI: 0.1-0.8) at baseline. The two groups did not differ otherwise at baseline. ICCs ranged between 0.76-0.94 for the static MRI-variables, 0.68-0.95 for the pharmacokinetic DCE-MRI parameters and 0.97-1.00 for the heuristic DCE-MRI variables.

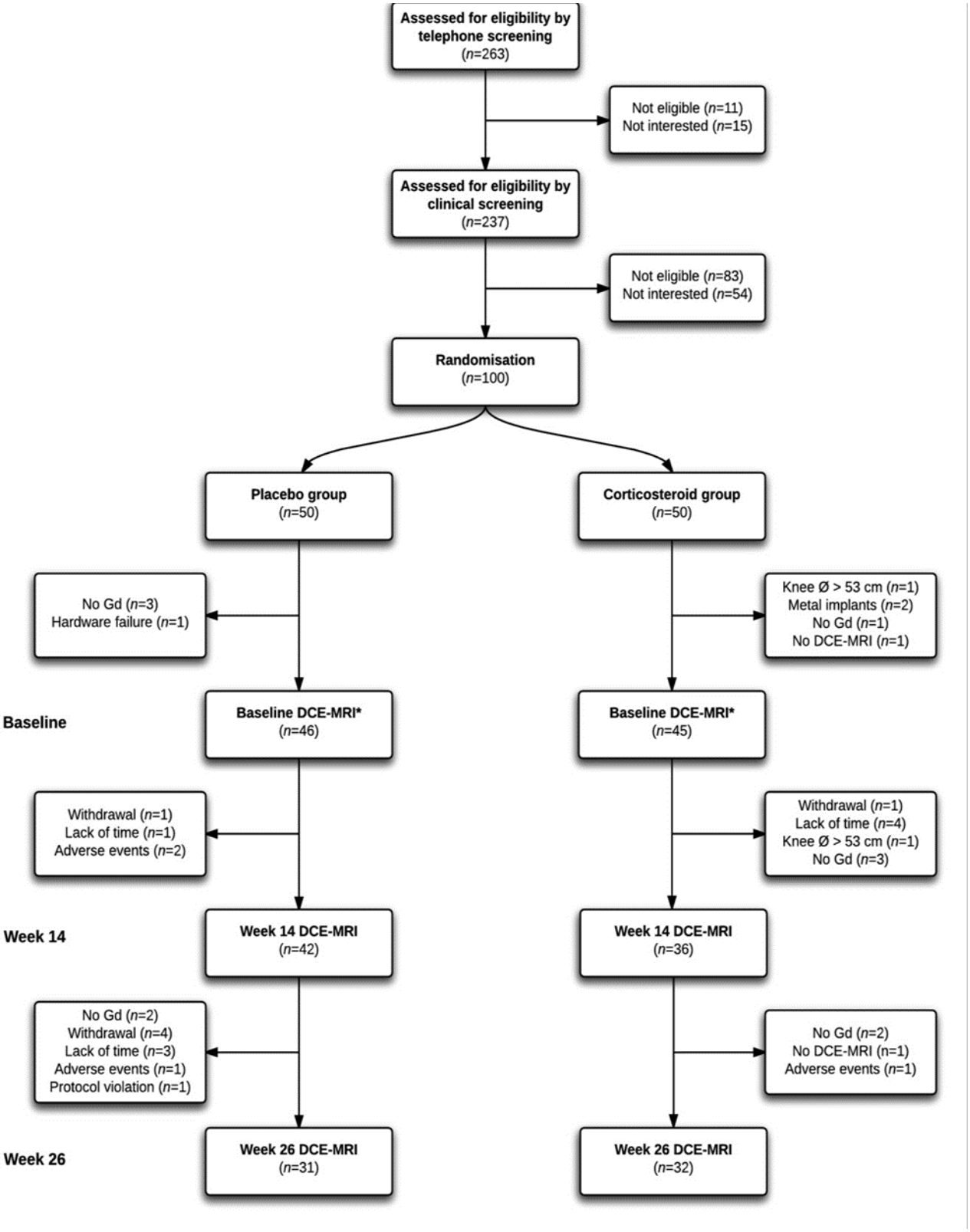
Changes in MRI-measures of synovitis (placebo vs. corticosteroid)
There was a statistically significant difference in the mean change in the static, non-CE-MRI

MOAKS-Synovitis at both week 14 (mean difference: 0.41, 95% CI: 0.09-0.73, p=0.01) and week 26 (mean difference: 0.57, 95% CI: 0.25-0.89, p<0.001) in favour of intraarticular corticosteroids (Table 10); however, there was no statistically significant interaction between the group and follow-up. There were no other statistically significant group differences in the MRI-variables (Table 10).

Associations between PROMs and MRI
At week 14, the primary endpoint, we found no statistically significant MRI-predictors of either of the

PROMs (Table 11). At week 26, CE-Synovitis was a statistically significant MRI-predictor of KOOSPain and KOOS-ADL indicating that an increase of one point in CE-Synovitis is associated with a worsening of 2.1 and 1.5 points in KOOS-Pain and KOOS-ADL respectively.

Figure 8. Trial profile



*modified intention-to-treat population (*n*=91)

Table 10. Changes in MRI-measures of synovitis.

Week 14 (Δ from baseline)	Intervention arm		Comparison	
	Placebo	Corticosteroid	Mean difference (95% CI)	p-value
MExNvoxel	-1.77 (-15.26 – 11.73)	-7.36 (-21.01 – 6.29)	5.60 (-13.63 – 24.83)	0.57
Nvoxel	-0.16 (-7.16 – 6.84)	-9.18 (16.26 – -2.10)	9.02 (-0.95 – 18.99)	0.08
IRExNvoxel	-0.047 (-0.169 – 0.075)	-0.018 (-0.142 – 0.105)	-0.03 (-0.20 – 0.15)	0.74
IRExME	-0.001 (-0.004 – 0.002)	0.00 (-0.003 – 0.003)	-0.001 (-0.005 – 0.003)	0.61
K_{trans}	0.003 (-0.003 – 0.010)	0.00 (-0.006 – 0.007)	0.003 (-0.006 – 0.012)	0.54
Ve	-0.001 (-0.034 – 0.019)	0.013 (-0.013 – 0.040)	-0.021 (-0.058 – 0.017)	0.27
iAUGC60	-0.003 (-0.012 – 0.006)	0.002 (-0.008 – 0.011)	-0.005 (-0.018 – 0.008)	0.45
MOAKS-Synovitis	0.03 (-0.19 – 0.25)	-0.38 (-0.61 – -0.16)	0.41 (0.09 – 0.73)	0.01§
CE-Synovitis	-0.50 (-1.18 – 0.18)	-0.91 (-1.60 – -0.23)	0.42 (-0.55 – 1.38)	0.40
BLOKS-Effusion	0.00 (-0.14 – 0.14)	-0.09 (-0.23 – 0.05)	0.09 (-0.11 – 0.29)	0.38

Week 26 (Δ from baseline)	Intervention arm		Comparison	
	Placebo	Corticosteroid	Mean difference (95% CI)	p-value
MExNvoxel	-3.27 (-16.76 – 10.22)	-3.83 (-17.47 – 9.82)	0.56 (-18.67 – 19.79)	0.95
Nvoxel	1.87 (-5.13 – 8.87)	5.91 (-12.99 – 1.17)	7.78 (-2.19 – 17.75)	0.13
IRExNvoxel	-0.114 (-0.237 – 0.008)	0.056 (-0.067 – 0.180)	-0.171 (-0.219 – 0.070)	0.31
IRExME	-0.001 (-0.003 – 0.002)	0.002 (-0.001 – 0.005)	-0.003 (-0.006 – 0.001)	0.25
K_{trans}	0.002 (-0.004 – 0.009)	-0.001 (-0.007 – 0.006)	0.003 (-0.006 – 0.012)	0.50
Ve	0.024 (-0.002 – 0.051)	0.022 (-0.004 – 0.049)	0.002 (-0.035 – 0.039)	0.91
iAUGC60	-0.003 (-0.012 – 0.006)	0.004 (-0.006 – 0.013)	-0.006 (-0.019 – 0.007)	0.35
MOAKS-Synovitis	0.12 (-0.11 – 0.34)	-0.45 (-0.68 – -0.23)	0.57 (0.25 – 0.89)	0.0006§
CE-Synovitis	-0.78 (-1.46 – -0.10)	-0.80 (-1.49 – -0.12)	0.02 (-0.94 – 0.99)	0.96
BLOKS-Effusion	0.04 (-0.10 – 0.18)	-0.02 (-0.16 – 0.12)	0.07 (-0.14 – 0.27)	0.52

§ p = 0.35 for interaction (week*group)

Table 11. Regression analyses—MRI vs. KOOS.

Week 14 (Δ from baseline)	Simple regression, potential predictors (p<0.10)		Multiple regression, significant predictors (p<0.05)	Adjusted multiple regression, significant predictors (p<0.05)
KOOS-Pain	N/A		N/A	N/A
KOOS-Sport/Rec	N/A		N/A	N/A
KOOS-Symptoms	MExNvoxel Nvoxel	-0.05 (p=0.07) -0.11 (p=0.07)	N/A	N/A
KOOS-QOL	CE-Synovitis BLOKS-Effusion Nvoxel MExNvoxel	-1.16 (p=0.06) -4.95 (p=0.08) -0.14 (p=0.01) -0.05 (p=0.04)	N/A	N/A
KOOS-ADL	CE-Synovitis	-1.06 (p=0.09)	N/A	N/A
Week 26 (Δ from baseline)	**Simple regression, potential predictors (p<0.10)**		**Multiple regression, significant predictors (p<0.05)**	**Adjusted multiple regression, significant predictors (p<0.05)**
KOOS-Pain	CE-Synovitis Nvoxel MExNvoxel iAUGC60	-2.17 (p<0.01) -0.11 (p=0.05) -0.06 (p=0.07) -87.27 (p=0.08)	CE-Synovitis -2.24(p=0.008)	CE-Synovitis -2.16 (p=0.01)
KOOS-Sport/Rec	CE-Synovitis Nvoxel IRExNvoxel	-1.48 (p=0.06) -0.12 (p=0.06) -6.25 (p=0.06)	N/A	N/A
KOOS-Symptoms	CE-Synovitis Nvoxel iAUGC60	-1.80 (p=0.01) -0.10 (p=0.09) -130.86(p=0.02)	N/A	N/A
KOOS-QOL	CE-Synovitis	-1.34 (p=0.03)	CE-Synovitis -1.34 (p=0.03)	N/A
KOOS-ADL	CE-Synovitis	-1.60 (p=0.01)	CE-Synovitis -1.60 (p=0.01)	CE-Synovitis -1.46 (p=0.02)

8. Discussion of findings

8.1. General considerations

There are some overall limitations in the three studies that need to be mentioned: studies I-II are crosssectional in design and thus have some inbuilt limitations most notably the fact that only an association but no causation can be inferred[223]. Secondly, in the same two studies (I and II) we were only able to draw ROIs around the synovium in the peripatellar recesses; thus the DCE-MRI parameters do not represent the entire synovium which may have influenced the results. Thirdly, in studies II-III we only assessed synovitis and did not include any other known pain-causing sources in KOA such as BMLs. Lastly, we chose to use the means of the DCE-MRI parameters from the entire volume of interest. Synovitis is heterogeneously distributed in KOA. By drawing ROIs covering as much of the synovium as possible and use the mean values, we may have caused *regression towards the mean* and thus overseen a potential effect on synovitis[224]. We deliberately chose to use the mean values, instead of the maximum values, as the improper inclusion of a vessel in the ROIs would have affected the maximum values substantially especially in smaller volumes of interest. Whether maximum values are more appropriate than mean values or if ROIs should only be drawn around the areas with the most severe synovitis on DCE-MRI are hypotheses that warrant more studies, as one may suspect that these areas, rather than the remaining synovium, are the driving force in the symptomatology and pathophysiology in KOA.

We used two different analytic DCE-MRI approaches, heuristic and pharmacokinetic, and both have their advantages and

disadvantages. Though some may argue that pharmacokinetic analyses are more appropriate from a physiological point of view as pharmacokinetic parameters reflect measures of perfusion (and not signal intensity), the heuristic DCE-MRI variables overall showed stronger correlations with histological synovitis (study I) and pain (study II) and no differences following an intervention with intraarticular corticosteroids/placebo and exercise (study III). In addition, the lack of a consensus on the optimal DCE-MRI sequence including its temporal resolution, and the numerous different published pharmacokinetic models, make it difficult to compare results across studies and centres. To the best of our knowledge, there are very few OA-studies[225] besides the three enclosed in this PhD that utilise both pharmacokinetic and heuristic analyses enabling a direct intra-subject comparison between the two analytic approaches regardless of the MRI-system. Nonetheless, which of the two analytic approaches is more appropriate in assessing synovitis in KOA remains to be fully elucidated.

Some of the major strengths of the three studies are the predefined statistical analyses, the consequent use of conventional static non-CE-MRI, conventional static CE-MRI and DCE-MRI including both heuristic and pharmacokinetic analyses and the overall relatively higher temporal resolution of the DCE-MRI sequence ranging from five to nine seconds compared to other studies using DCE-MRI in both KOA225 and RA144, 226.

8.2. Study I

The main finding in study I is that only the heuristic DCE-MRI variable MExNvoxel showed a correlation with histological synovitis stronger than the pre-specified threshold of significance of r≥0.70. MExNvoxel reflects both the volume of the most perfused synovium (Nvoxel) and the degree of perfusion (ME); similarly the microscopic score is a composite score based on an increased volume
(thickening of the synovial lining, oedema and cellular infiltration) and a measure of vascularity (number of endothelial cells) in the synovium. Only few studies have investigated the association between histological synovitis and synovitis assessed on DCE-MRI in KOA: Loeuille et al. only found an association between a high rate of enhancement in the synovium and vascular congestion, but none of the remaining subscales or the composite histological synovitis score[46]. Østergaard et al. found a statistically significant correlation between the early rate of enhancement and histological synovitis but in a mixed population of OA and RA[213].

In the second part of the analyses, we found that the addition of first CE-MRI variables increased R^2 to 52% (from 39%) and by further offering the DCE-MRI variables the maximum R^2 yielded was 71%. R^2-value (if unadjusted) is dependent on the number of variables included, i.e. the greater the number of variables the higher R^2. In this study however, the final model consisted of only four variables (gender, CE-Synovitis, IRExNvoxel and iAUGC60) which all contributed significantly to the model.

8.2.1. Strengths and limitations

To the best of our knowledge, study I is the first study to investigate the association between histological synovitis in KOA and synovitis assessed on MRI, using non-CE-MRI, CE-MRI and DCEMRI with both heuristic and pharmacokinetic analyses. As the study included several MRI-variables, we pre-defined a threshold of significance of r ≥ 0.70 in the correlation analyses, i.e. we would only consider strong or very strong correlations as statistically significant.

As synovitis is heterogeneously distributed in KOA, we aimed at covering as much of the synovium as possible by obtaining synovial biopsies from six different locations and using whole-knee scores in both the macroscopic and conventional static MRI-assessments of synovitis. The drawing of the ROIs was however only possible in the peripatellar regions and thus constitute a limitation of the study. In addition the study was conducted on patients with end-stage KOA and may not reflect earlier stages of the disease as synovitis in early and late OA may differ histologically[50].

8.3. Study II

In study II, we demonstrated that peripatellar synovitis assessed on non-CE-MRI, CE-MRI and DCEMRI is correlated with pain. The correlations with pain ranged from -0.21 to -0.37 and were thus only weak-moderate but nonetheless comparable with—and to some extent stronger than—the ones found in a similar study using CE-MRI[54]. In the regression analyses, MExNvoxel was the strongest explanatory DCE-MRI variable. Interestingly, the non-CE-MRI variable MOAKS-Effusion, and not CE-Peripatellar (synovitis assessed on CE-MRI), was the strongest explanatory conventional static MRI-variable. This was rather surprising as it is generally accepted that synovitis is optimally assessed on CE-MRI. A possible explanation may be that MOAKS-Synovitis represents the combination of synovitis and effusion in the suprapatellar recess and both synovitis and effusion are known to be associated with pain[18].

8.3.1. Strengths and limitations

Besides the aforementioned limitations, the results may have been influenced by selection bias as the study population had statistically significant lower body weight, BMI and KL-grades than the dropouts. Our study population consisted predominantly of obese, female subjects and thus not entirely representative but may very well reflect the typical KOA-patient[227].

The major strengths of this study are its relatively large size in terms of MRI-studies in KOA, the use of a 3T MRI-system and the high reproducibility of the applied image analyses.

8.4. Study III

Study III was designed to evaluate the effects of exercise and intraarticular corticosteroids/saline on synovitis assessed with MRI. Overall, there were no statistically significant differences between the two interventions in regards of MRI-measures of synovitis as was the case with ultrasound-measures of synovitis[228] and measures of pain senstivity[229]. This may (partially) be due to the relatively low dose of 40 mg prednisolone and the long follow-up of 14 weeks as the effects of corticosteroids are shortlived. Three recent observational KOA-studies found a decrease in MRI-measures of synovitis following an injection

with 80 mg prednisolone with a median time between baseline and follow-up of eight[55, 225] and 20 days[56] respectively. A follow-up of one-two weeks would presumably have been more appropriate in order to detect an effect on MRI.

In the regression analyses, we found no statistically significant MRI-predictors of either of the PROMs at week 14, the primary endpoint. In other words, the improvement in pain and function the participants experienced could not be explained in a change in synovitis. However at week 26, CESynovitis was a statistically significant MRI-predictor of KOOS-Pain and KOOS-ADL indicating that an increase of one point in CE-Synovitis is associated with a worsening of 2.1 and 1.5 points in KOOS-Pain and KOOS-ADL respectively. It is interesting to notice that the effects of CE-Synovitis only become evident at week 26—this may however also be due to multiple statistical tests and chance findings and thus warrants further investigations.

An overall decrease in synovitis assessed on CE-MRI (CE-Synovitis) in both groups was observed at week 26 (and week 14 for the corticosteroid group). Even though reduction of synovitis on US following intra-articular placebo has been described[230], we believe that this effect is due to the exercise programme rather than the intraarticular injections. This indicates a synovitis-reducing effect of exercise that persists even 12 weeks after the termination of the programme. Hunter et al. recently investigated the effects of diet, exercise and diet and exercise combined on structural outcomes assessed on non-CE-MRI and radiographs in KOA. The authors found no difference between the groups regarding changes in synovitis (or any other structural outcome) but the analyses were conducted with the exercise group as control/reference and the changes in synovitis in the exercise group were not reported[231]. Whether exercise has an additional beneficial effect on synovitis and not only pain and function needs to be confirmed in future studies.

8.4.1. Strengths and limitations

The major strength of study III is its rigorous study design including measures to reduce bias and the pre-specified statistical analysis plan. In addition, we were able to assess the entire synovium on nonCE-MRI, CE-MRI and DCE-MRI. Besides the length of the follow-up, another important limitation is that the study was designed and powered to measure changes in the PROMs and not MRI-measures which may have influenced the results. Furthermore, at baseline the placebo group was on average older, with more severe radiographic KOA and more effusion on CE-MRI (BLOKS-Effusion) which thus constitutes a risk of selection bias.

9. Conclusion

The studies, which form the basis of this thesis, have extended the current knowledge of synovitis and the role of MRI in assessing synovitis in KOA.

The histological assessment of synovitis from biopsies remains the gold standard but is not routinely feasible. Thus, the development of a non-invasive method to assess synovial histology is relevant. In study I, we found a strong and statistically significant correlation between histological synovitis and the heuristic DCE-MRI variable MExNvoxel. Furthermore, by offering the DCE-MRI variables we were able to explain substantially more of the variability of histological synovitis compared to conventional static MRI. Thus, DCE-MRI provides additional information about synovial histology that is not captured on conventional static MRI.

In study II, we showed that all MRI-variables but one were statistically significantly correlated with pain. MExNvoxel was also the strongest explanatory DCE-MRI variable of pain, indicating that the variable is not only associated with histological synovitis but also pain. In general, the DCE-MRI variables showed stronger correlations with pain than the conventional static MRI-variables.

In study III however, the long-term improvement in pain and function following an intervention with intraarticular corticosteroids/saline and exercise could not be explained by concomitant improvement in any DCE-MRI-measure of synovitis.

In conclusion, DCE-MRI-measures of synovitis seem to be superior to conventional static MRI in regards of their association with histological synovitis and pain in a cross-sectional setting. However the use of DCE-MRI over conventional static CE-MRI cannot be justified when assessing the longterm changes in synovitis following an intervention with intraarticular corticosteroids/placebo and exercise.

10. Perspectives

Even though we could not detect any long-term changes in the DCE-MRI variables following an intervention with intraarticular corticosteroids/placebo and exercise, several studies have shown that DCE-MRI is a more sensitive tool than conventional static MRI in detecting changes in synovitis following treatment with e.g. corticosteroids in both OA[56, 225] and RA[145] and biological disease modifying anti-rheumatic drugs in RA[232]. DCE-MRI could therefore play a role in the development and assessment of new anti-inflammatory, synovitis-reducing drugs in KOA. Furthermore, the addition of a DCE-MRI sequence to a CE-MRI protocol is feasible on most MRI-systems.

Evidence is mounting that KOA is constituted of different phenotypes[233] and there is an urgent need to define these in order to improve and individualise treatment and management[234]. Berenbaum et al. suggest four different phenotypes: post-trauma OA, metabolic syndrome associated OA, ageing senescence-associated OA and crystallopathy-associated OA[16] but other classifications have been proposed[235, 236]. Whether these phenotypes are the only ones is uncertain and warrants more research. Nonetheless there is a need to better describe and understand the different processes taking place in (K)OA on an individual level and in the different stages of the disease. DCE-MRI may very well be a useful tool in these challenges especially in regards to perfusion and inflammation.

No single imaging or biochemical tool that can characterise the entire osteoarthritic joint has been developed. The different investigative tools all provide us with different information and complement each other. Our challenge as researchers is to combine the different tools in order to gain a better understanding of the disease, define and characterise the different types of OA and ultimately develop not only an efficient and

disease modifying treatment for KOA but also a prognostic tool for the development of KOA and symptomatic outcome after intervention such as TKA.

11. Summary

Knee osteoarthritis (KOA) is one of the most common causes of physical disability in the elderly population. With an increasing ageing and obese population, the prevalence of KOA is expected to rise substantially. The needs for a better understanding of the disease and tools that can predict the course of the disease, for example following treatment, are therefore imperative.

Inflammation has over the last years been recognised as an important factor for both the symptomatology and disease course in KOA. Synovitis, inflammation of the synovium, is the hallmark of intra-articular inflammation and has been associated with pain, symptoms and disease progression. Synovitis can be visualised on conventional static MRI. However, the addition of a dynamic contrastenhanced (DCE) MRI-sequence enables the assessment of the synovium both in regards of its morphology and perfusion. Studies in both KOA and rheumatoid arthritis have shown that DCE-MRI measures of synovitis are more sensitive than conventional static MRI in regards of microscopic synovitis and patient-reported outcome measures (PROMs).

The aims of this PhD project were to characterise synovitis in KOA with conventional static and dynamic contrast-enhanced MRI in regards of histology (study I), its association with PROMs (studies II-III) and changes following a symptoms-improving intervention (study III). We found that DCEMRI-measures of synovitis seem to be superior to conventional static MRI in their association with histological synovitis (study I) and pain (study II) in a cross-sectional setting. However, the use of DCE-MRI over conventional static CE-MRI cannot be justified when assessing the long-term changes in synovitis following an intervention with intraarticular corticosteroids/placebo and exercise (study III).

Evidence is mounting that KOA is constituted of different phenotypes. There is an urgent need to define these in order to improve and individualise treatment and management. It is essential to gain a better understanding of the different processes taking place in KOA, on an individual level and in the different stages of the disease. DCE-MRI may very well be a useful tool in facing these challenges especially in regards of the role of perfusion and inflammation in KOA and osteoarthritis in general.

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