MRI in Knee Osteoarthritis

Application in diet intervention

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THE THREE ORIGINAL PAPERS

I. Gudbergsen H, Lohmander LS, Jones G, Christensen R, Bartels EM, Danneskiold-Samsøe B, Bliddal H and Boesen M. Correlations between radiographic assessments and MRI features of knee osteoarthritis - a cross sectional study. Osteoarthritis and Cartilage 2012.
II. Gudbergsen H, Boesen M, Lohmander LS, Christensen R, Henriksen M, Bartels EM, Christensen P, Rindel L, Aaboe J, Danneskiold-Samsøe B, Riecke BF and Bliddal H. Weight loss is effective for symptomatic relief in obese subjects with knee osteoarthritis independently of joint damage severity assessed by high-field MRI and radiography. Osteoarthritis and Cartilage 2012;20:495-502.
III. Gudbergsen H, Boesen M, Christensen R, Henriksen M, Bartels EM, Danneskiold-Samsøe B and Bliddal H. Changes in bone marrow lesions in response to weight loss in obese knee osteoarthritis patients: A prospective cohort study. Submitted.

BACKGROUND

Introduction

Knee osteoarthritis (KOA) was traditionally believed to be a strictly mechanical disease which originated from wear and tear on especially cartilage. The model of KOA has changed dramatically in the recent years and is presently considered a disease influenced by genetics, age, biomechanical stress, biochemical changes and environmental factors [1-6]. This has changed the perception of KOA, which is now considered to be a whole organ disease that affects all structures comprising the knee joint, including cartilage, bone, bone marrow, ligaments, menisci and joint capsule.
KOA occurs when the inherent processes in the synovial joint are put off balance resulting in change of the previously maintained equilibrium. Hereby increases the joint stress and this leads to functional and structural failure [7]. Humans are susceptible to developing KOA due to genetic and environmental factors [2] and changes caused by these factors may eventually result in clinical and/or paraclinical manifestations.
KOA patients often present themselves with one or more of the following items, that may be divided into patient specific complaints (pain, stiffness, loss of function, joint swelling) and/or features found at the clinical examination (muscle weakness, bony formations, joint tenderness, crepitus, instability and painful and/or reduced range of motion) [8]. At this point, patients present with a wide variety of structural changes in the knee, including osteophyte formation, cartilage loss, sclerosis, effusion and synovitis. KOA may further be accompanied by a malaligned knee joint axis [9]. The variations in phenotype as well as the inconsistency between patient's complaints and pathological findings with imaging are not yet clarified [10].
The following sections give an account of what is presently known on topics relevant as the background for this thesis.

Impact of KOA

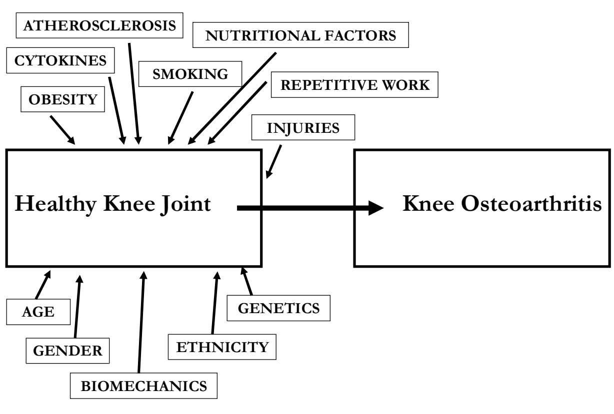
The most prevalent type of arthritis is KOA [10,11] and as the incidence of obesity is escalating, this causes an increased accumulated prevalence of both illnesses [12,13]. The KOA-related symptoms have a major impact on subjects social and physical wellbeing, and KOA is expected to be the fourth leading cause of disability in 2020 [12,14]. This in turn may lead to inactivity and thereby an increased morbidity and mortality [15]. The perspective seen from the Danish health services is that of the 1.5 million citizens above the age of 54, an estimated 10 % have KOA and 50 % of these are concurrently troubled by obesity [6]. At the patient specific level evidence suggests that normal knee functioning is particularly important for elderly citizens, and that musculoskeletal diseases leads to loss of physical function and to a dependency of health care [16-18].

Aetiopathogenesis

KOA is clearly a multi factorial disease and the aetiopathogenesis includes local factors (trauma, malpositioning, overloading, muscle weakness around joints etc.), general conditions (old age, female sex, obesity, physical activity level) together with genetic susceptibility [2,19,20].
The relative contribution of these factors, and their importance for development and progression of KOA with possible implications for sub grouping remains to be clarified.
As people age, the prevalence and severity of radiographic KOA (RKOA) increases [20,21] and estimates are that 20 % of all patients aged 45 years or older have KOA and that this increases to 35 % in subjects age 65 years or older [21,22]. However, the prevalence of symptomatic KOA is significantly less, while also increasing with age [22].

Obesity is recognized as a very important risk factor for KOA [23], a high body mass index (BMI) has been found to increase the risk of KOA and weight-loss to reduce this susceptibility [2,24,25]. KOA related symptoms tend to worsen in obese people with KOA [26], and KOA-related symptoms can be improved by weight-loss [27,28]. Furthermore, cytokines from adipose tissue have been independently linked to KOA [29].
The genetic predisposition for KOA is described in several studies and though very heterogeneous, the heritable component has been estimated to be significant [30]. Specific genetic sites have been reported to increase both prevalence and incidence of KOA [30], and in a recent metaanalysis the importance of one specific allele was confirmed [31]. The genetic influence in terms of clinical outcomes is not yet well examined. Ethnicity has been shown to influence the prevalence of KOA which may be due to differences in the anatomical shape of bones [32].
Knee joint injuries [33,34] and repetitive work, especially squatting and lifting [35], are well known risk factors for development of KOA.
Males have a reduced prevalence and incidence of radiographic and symptomatic KOA, compared to females, and also, females are likely to have more severe KOA [21,22]. The incidence of females with KOA rises dramatically after the climacteric transition [22], however, research in whether or not the dissimilarity could be explained by hormonal difference did not show significant results to support this hypothesis [36,37].
Local biomechanical changes include joint laxity, muscle strength changes, limb length inequality and malalignment and these factors interact in a not fully clarified manner [9,38,39]. Muscle weakness has been associated with incident KOA [40], described to predict onset and progression of KOA, and is a very important risk factor for the future physical function in patients [41]. There are conflicting data on the importance of alignment with respect to incident KOA [42,43] while alignment seems important in terms of KOA progression [42]. Limb length inequality seems to be important in KOA research but further research is needed before conclusions can be made [39].
Furthermore, research suggests that risk factors for KOA includes nutritional factors [44,45], bone mineral density [46], level of physical activity [47], antioxidants [48], as well as smoking [49] and recent studies also imply a role of cytokines and atherosclerosis [29,50-52] (figure 1).

Figure 1. Risk factors for Knee Osteoarthritis.



Diagnosis of KOA

In order for patients to by diagnosed with KOA, researchers and clinicians rely on three main definitions, as given below, and in total at least 25 different classification systems can be found in the existing literature [53]. The radiological definition of KOA is based on assessments of structural damage [54,55] with the most applied method being the KL assigning a total knee joint score from 0 to 4 by comparing joint damage to a radiographic atlas [56]. The clinical definition, as defined by e.g. the ACR criteria, is addressing the cardinal symptoms and signs of KOA [57].
The combined radiographic and clinical definition of KOA is based on clinical symptoms and radiographic changes, also defined by the American College of Rheumatology (ACR). There are apparent discrepancies between these definitions [58,59] as well as discordance between researchers using them [60]. Several scoring systems for Magnetic Resonance Imaging (MRI) (KOSS, WORMS, BLOKS and MOAKS, please see abbreviations) have existed for years [61-64], but it was not until august 2011 that an actual definition of KOA based on MRI was presented [65]. Future trials are now recommended to test its diagnostic performance.
Clinicians often collect data on known risk factors and supplementary clinical features to either strengthen of weaken their confidence of a diagnosis [8]. Imaging is here often used to support an initial examination. However, recent recommendations from the European League against Rheumatism (EULAR) have actually discarded the use of conventional radiography (CR) for an initial diagnosis of KOA and state that a background history, clinical examination and symptomatic assessment are sufficient for most diagnostic purposes [8].

Symptoms

KOA related symptoms are a major cause of disability and patients complaints of pain, joint tenderness and movement limitations are central outcomes in KOA research [7]. Pain is without doubt the primary concern for most patients and the following section takes this into account. An inconsistency between symptoms and imaging [20,66-68] and the prevalence of asymptomatic RKOA [67,69] are important aspects when discussing the subject of why some knees hurt and others do not [7,70].
The discussion of pain in KOA often starts with cartilage. Damage to this knee joint structure is the hallmark of KOA, but as cartilage is aneural and avascular it is unlikely that changes detected in this structure have a significant and direct impact on pain-related symptoms [71]. The attempt to treat KOA with intra-articular anaesthetics and the resulting absence of pain relief for all patients supports the notion that symptoms, to some extent, origin from extra-synovial knee joint structures [72]. Partly defect cartilage surfaces still protect the subchondral bone, in which the free nerve endings are located, and this could explain why some patients do not experience pain. However, as the cartilage matrix degrades this may impact on changes in the subchondral bone and soft tissues, and thereby have an indirect impact on symptoms.
Based on earlier research, as well as on given theories, a series of other knee-joint structures [33,72,73] and KOA-related features [4,74,75] have been suggested to be linked to KOA symptoms. However, a recent review concluded that only synovitis and bone marrow oedema like lesions (BMLs) could be shown to have an association to KOA symptoms, and results originated primarily from cross-sectional studies [68]. BMLs are a common finding in painful osseous conditions [76] and have been proposed to consist of extracellular fluid that causes pain via an increased intraosseous pressure [77,78]. Synovitis involves a number of changes in

the synovial tissue which are involved in the generation of noxious stimuli, e.g. activation of synovial cells, synovial cell hyperplasia, release of prostaglandins, cytokine release as well as lymphocyte infiltration [7]. These changes are likely to have an impact on patient symptoms through soft tissues, including the frequent site for synovitis, Hoffa's fat pad [73].
Focusing on the relationship between radiography and clinical symptoms research has generally found a small or no association between RKOA and symptoms [67,79]. Even so, one analysis has found that the relationship between RKOA and symptoms was increased by a high level of study quality, the inclusion of the skyline views and by including elderly patients in a cohort with a high level of RKOA severity [79].
As patients are subjected to KOA symptoms over a long period of time, evidence supports that patients might face peripheral joint sensitization as well as plasticity changes in the central nervous system [80]. Furthermore, the subjective experience of pain is influenced by cognitive, social, emotional and behavioural factors; e.g. expectations, general anxiety and previous experience [81].

Interventions

The primary goals for treatment of patients with KOA are to reduce pain, improve daily function and physical ability, halt structural deterioration, and educate patients to cope with symptoms of KOA [82,83]. Methods to achieve this may be divided into four categories: conservative methods, pharmacological treatments, injections and surgical approaches [83]. Typically, surgical treatments are adapted to the specific anatomical site(s) of KOA whereas the conservative, pharmacological and injection-based treatments can be applied more generally.
Overweight KOA patients are recommended to lose weight as evidence support an effect on both physical function and symptoms of pain [27,28] and this treatment is now recommendable for obese KOA patients [83-85]. A weight reduction of 10 % and above has been shown to significantly improve the KOA-related symptoms [86] regardless the severity of KOA related structural and functional changes [87,88]. The single most important factor for achieving weight loss is to establish a continuous energy deficit and if a large initial weight-loss is achieved this is associated with a better prognosis for sustained weight-loss [84,89,90].
Exercise is considered to be an effective intervention for improvement of KOA-related symptoms, and evidence supports both conventional aerobic (usually walking) and aquatic-based training [83,91]. Muscle strengthening is considered to be a relevant target for therapeutic intervention as it may alter gait mechanisms and the external knee adduction moment (KAM) [92]. Evidence supports that modification of muscle strength has effects on clinical symptoms and physical function [4,85].
Conservative biomechanical approaches include the use of footwear that mimics barefoot movements, using full length lateral wedge insoles [93], utilize gait modifications [92] and applying valgus inducing knee braces [93].
The pharmacological approach includes prescription of mild analgesics such as acetaminophen, cyclooxygenase-2 (COX-2) inhibitors and other non-steroidal anti-inflammatory drugs (NSAIDs), and recent evidence also supports effects of opioids [94,95]. Besides these well-known therapeutic agents, trials are examining the effects of doxycycline, bisphosphonates and several nutraceuticals [95,96].
Intra-articular interventions is primarily performed with the use of corticosteroids, having a clear effect on symptoms on short and medium term, and hyaluronic acid, which effect at present is unclear [85,95,97].
Surgical interventions include debridement, osteotomy, unicompartmental knee arthroplasty, a minimal invasive unicompartmental knee implant (Unispacer) and total knee joint replacement (TKR) [85,98,99].
Most intervention studies also include self-management tutoring, and various forms of patient education and these aspects, along with a stepwise and patient-focused approach, are crucial to consider in any treatment procedure against this disabling and chronic disease [100]. Combining different recognized treatments in the design of intervention protocols is the aim for many trials [82] and future research is likely to examine the optimal setup for multi-modality interventions targeting the often numerous challenges KOA patients experience.

Aim and hypotheses

The aim was to examine the effects of joint malfunctioning in relation to the clinical benefits of a diet intervention and to investigate the impact of weight-loss on changes in MRI assessed BLOKS variables.
The thesis examines two main hypotheses, which are considered in the ensuing studies.
Obese knee osteoarthritis patients can achieve symptomatic improvements following diet intervention regardless of their level of structural damage and overall joint malfunctioning
Rapid weight-loss in obese patients with knee osteoarthritis will lead to improvements in KOA related pathology that can be assessed and evaluated by MRI.
In order to assess relevant imaging markers for use in KOA monitoring, the thesis included reliability assessments of internationally recognized quantitative and semi-quantitative scoring methods for imaging assessments of knee joints. By doing so it was the intention to make our findings directly comparable with earlier and future studies within this field of KOA research.

ASSESSING KNEE OSTEOARTHRITIS

Present research in KOA is focused on identifying disease-modifying osteoarthritis drugs (DMOADs) with effects on KOA-related clinical and paraclinical parameters, and preferably on both [95,96].

Conventional radiography

Currently, radiographs are the most widely applied imaging method for examining and diagnosing KOA. A frequently applied method is the Kellgren & Lawrence (KL) grading system [55] which applies a categorical grading scale from 0 to 4 and incorporates the evaluation of osteophytes, joint space narrowing (JSN), sclerosis and altered bone shapes (figure 2).

Controversies on the use of KL exist, often based on the fact that the grade relies too much on osteophytes and JSN and does not respond to early KOA joint damage. Osteophytes and JSN are without doubt important in the radiographic grading of KOA, but some studies have described that osteophytes can be present in patients without any visible cartilage damage and that detectable decreased mJSW is accompanied with serious cartilage loss [58,101]. Furthermore, due to various definitions of the KL grade and different imaging protocols, which are factors known to have high impact on classification and sensitivity, there is still no overall agreement on the uniform definition of RKOA [60,102].

Figure 2. The original Kellgren & Lawrence description.

Grade 0; No KOA	Grade 1; Doubtful	Grade 2; Mild	Grade 3; Moderate	Grade 4; Severe
No KOA	Doubtful narrowing	Possible narrowing	Definite narrowing	Marked narrowing
	+	+	+	+
	Possible osteophyte	Definite osteophyte	Multiple osteophyte	Large osteophyte
			+	+
			Possible Bone Deformity / Some Sclerosis	Definite Bone deformity / Severe Sclerosis

As a last point, KL categories are not equidistant and the degree of deterioration acquired for a patient to change category is often too large, even with follow-up periods of one year or more. Adding together, KL seems to have limited use as a primary imaging outcome for longitudinal trials [103].

The other major method used for assessing the degree of KOA damage is by measuring the minimum joint space width (mJSW) which is presently the most widely accepted imaging method for assessing the outcome of a clinical trial [104-106]. Radiographs visualize the bone structures and by measuring mJSW one can indirectly assess the conditions of soft tissues between two bone surfaces. The literature describes several methods for obtaining radiographs that can be used for measuring mJSW [54] and these can be divided into four major types in weight-bearing conditions; full-extension view, semi-flexed view, fixed semi-flexed view, and fluoroscopically guided semi-flexed view. The reproducibility of the three latter recommended methods are good, with coefficients of variation being 1.3, 4.3 and 3.5 %, respectively [54,107,108]. As changes are considered to be small in any trial setup, precision in measurements of mJSW is very critical, and mJSW has been criticised as a measure in both cross-sectional and longitudinal studies [104]. Other results support the method as being reliable [109].

Radiographic scoring methods are cheap, quick and commonly accessible, but CR is associated with several limitations and potential drawbacks (ionizing radiation, risk of changed positioning, low reproducibility of x-ray beam alignment and examination in 2D). Overall, CR cannot detect early pathological changes in KOA, occurring primarily in the soft tissue, and CR-based grading systems therefore have an inherent high specificity but low sensitivity [110]. Furthermore, it typically takes several years for the radiographic scores to change [106].

The above mentioned considerations exclude CR from being the only imaging modality in most clinical trials and explain some of the reasons why most clinical trials aim to include MRI in their imaging protocol. Additional reasons are that a series of affected knee structures in KOA cannot be assessed on CR. MRI is therefore considered to be the most promising imaging modality when evaluating joint structures in KOA [111].

Magnetic resonance imaging

Field strength of MRI scanners are important, but low- and high field MRI can both be used to assess knee joint pathology as these techniques both provide additional information to radiographs regarding soft tissue changes. In general, the signal to noise ratio (SNR) will increase with field strength whereas the contrast to noise ratio (CNR) remains relatively unaffected by field strength [112].

The advantages of low-field MRI scanners are low costs and easier installation along with being more tolerable for claustrophobic patients. The main disadvantage of low field MRI is a reduced image quality due to lower SNR and this is often dealt with by reducing matrix and bandwidth or by increasing field of view (FOV), NEX, TR and slice thickness. Unfortunately, any adjustment will impact on resolution, SNR and scan time and could be the reason for an increasing level of motion artefacts. Recent studies on the subject of whether or not field strength is significantly important in musculoskeletal imaging suggested low-field imaging to be inferior with respect to the assessments of minor cartilage damages and anterior cruciate ligament pathology [113,114]. Even so, the authors also commented that the area was not sufficiently examined to make firm conclusions.

MRI provides excellent contrast resolution between soft tissues and is the preferred imaging method in the field of KOA research, allowing evaluation of several important pathological features of KOA and to accomplish a whole organ assessment of the knee [115]. The modality is advantageous to CR because it is reproducible, poses no radiation hazard, and can detect structural changes at an earlier stage of disease stage in 3D [110].

Regardless of the amount of sophisticated techniques presently available, it remains crucial to select an optimal MRI protocol to obtain the best possible scan result.

MRI has been through a tremendous development within the musculoskeletal area and it is now possible to assess joint conditions both qualitatively and quantitatively [116-119]. For the assessment of knee-joints one may apply a variety of field strengths (3.0, 1.5, 1.0 and 0.2 T) and when scanning, it is common to apply a combination of 2D SE, and 3D gradient echo (GRE) sequences developed to show cartilage [120-123] and other relevant structures [105,118,124-126].

Several well-described protocols for imaging cartilage, BMLs, synovitis etc. have been published [105,118,124,126,127] enabling assessments of all KOA relevant knee joint structures [116,117,119,128]. The above described considerations were all taken into account as the MRI protocols for the trials behind this thesis were developed, but we also considered the following: i) available imaging equipment, ii) skill and capability of radiologist and radiographic technicians, iii) patient safety and comfort, iv) costs and v) the best possible way of visualizing selected knee joint structures [118]. All considerations were taken into account when choosing the final MRI protocol. Current KOA-related MRI-research is focused on developing and applying different objective and semi-objective methods to assess joint conditions for diagnosing and monitoring KOA. Among these methods are grading systems for assessing the knee joint as a whole (KOSS, WORMS, BLOKS or MOAKS) [61-64], ways of quantifying cartilage (qMRI) [121,129], evaluation of cartilage morphology [130] and surface curvatures [131]. Several groups have examined methods to characterize cartilage quality [132]. BLOKS is one of many grading systems for MRI assessments of KOA [61]. It divides the knee into nine intra-articular regions and contains eight items, including BMLs, cartilage abnormalities, synovitis, osteophytes, effusion, ligament damage, and meniscal pathology, that are graded semi-quantitatively.

BLOKS is considered to be an important tool for whole-joint assessments of the knee, and collecting data on all KOA relevant

structures provides additional and important information compared to radiographs and qMRI [133,134].
BMLs are characterized as ill-defined hyper-intense areas on MRI [61,126] and are believed to consist of fibrosis, necrosis, inflammatory cells and a variety of other pathological abnormalities [78]. BMLs have repeatedly been shown to predict cartilage loss and overall progression of disease [135,136], and have been associated to clinical symptoms [68]. However, even though BMLs and especially large BMLs have been related to prevalent knee pain [72,77,137,138], longitudinal trials have failed to associate changes in BMLs to concomitant changes in clinical symptoms [139]. Progressions of semi-quantitative scales for assessing cartilage pathology have been linked to gender, age, BMI, osteophytes, tibial bone area, and overall volume [140]. Specific signal alterations on MRI have been verified to represent synovitis [141], and recent evidence suggests that synovitis plays a separate role in KOA, as well as being a secondary phenomenon [134]. Synovitis has been shown to correlate well with pain, and changes in the degree of synovitis have been associated to changes in pain symptoms [142]. Effusion is believed to result from a synovial activation or inflammation due to a secondary structural damage, and evidence suggests that effusion is correlated to KOA severity and clinical symptoms [138,143]. The role of osteophytes, evaluated on MRI, is to our knowledge not investigated. Cruciate ligament damage changes knee joint kinematics, especially in the medial chamber, and has been associated to the incidence of KOA as well as progression. The relationship between symptoms and ligament damage is not yet completely clarified [134].
Normal function of the menisci is critical for maintenance of equilibrium in the knee joint, and understanding meniscus pathology is critical for the understanding of KOA [33,144]. Extrusion, tears and signal changes in menisci have all been linked to increased incidence and progression of KOA, BMLs, cartilage volume loss and level of symptoms [145-147].
qMRI has the potential of monitoring changes in the volume of joint cartilage and is currently accepted as a valid and reproducible method of examination [105,121]. In patients with radiographically verified KOA and clinical symptoms of disease, studies present data of an annual cartilage volume loss of approximately 3-5 % [148,149], compared to the normal loss of cartilage volume in comparable patients without KOA being 2-3 % [37,150]. Risk factors for cartilage loss are BMLs, female gender, bone size, cartilage defects, high cartilage volume, meniscal pathology, and an increased level of clinical KOA symptoms [115,147,149,151].
The loss of cartilage volume is larger in the weight-bearing areas, and this loss correlates with joint space width, high KL, increased BMI and a high degree of pain symptoms [147,152]. Obesity and accelerated loss of cartilage both correlate to an increased risk of future TKR [153,154].

The delayed gadolinium enhanced MRI of the cartilage (dGEMRIC) method is based on the T1-relaxation time following a delayed diffusion of gadolinium into cartilage. It has the ability of giving a more precise estimation of cartilage matrix composition of GAG and is therefore one of the most promising techniques in future KOA assessments [119,127].
dGEMRIC is easily applicable in the modern state of the art MRI scanners, and the result comes with a high resolution and sensitivity as well as a clear demarcation of cartilage boundaries [119,155]. But still, the post-processing part is tedious and complicated when analysing larger cohorts. Glycosaminoglycan (GAG) content measured by dGEMRIC corresponds to biochemical and histological measures of GAG [156], and studies have revealed a high level of inter- and intra-reader reproducibility [157]. In addition, GAG content measured by dGEMRIC has been shown to correlate with KL, degree of malpositioning [158], and level of physical activity [119,159].

Muscle strength

Generally, adequate muscle strength is critical to maintain normal function of the knee joint [74] and is known to be associated with clinical symptoms in KOA [4,70,160]. Results have shown that patients with KOA have decreased muscle strength compared to healthy controls [41], and muscle weakness is associated with a decrease in function and a higher level of pain [4,70,161].
Strengthening of muscles has been shown to improve clinical symptoms and the functional performance of KOA patients [85,160] but the relationship of these findings is not clear [162]. These findings have been confirmed in experimental knee pain studies [163]. The muscle weakness observed in KOA patients is presumably caused by arthrogenic muscle inhibition elicited by joint pain [164] and seems primarily to arise as a consequence of KOA.

Frontal plane knee alignment

The mechanical knee joint alignment axis is measured as the angle between the intersection of the tibial and femoral axes. The tibial axis is located as a line from the centre of the tibial plateau to the centre of talus and the femoral axis is located as a line from the femoral head to the intercondylar area. The literature suggests that alignment is closely associated to KOA severity, especially in obese subjects [165], but the causality between alignment and KOA is unknown. Malpositioning of the knee joint has been revealed as a significant predictor for progression in KOA disease assessed by both radiographs and MRI [9,166]. Furthermore, alignment is highly correlated to the high KAM [167] which reflects the compressive forces of the medial compartment and is closely associated to development of KOA [92].

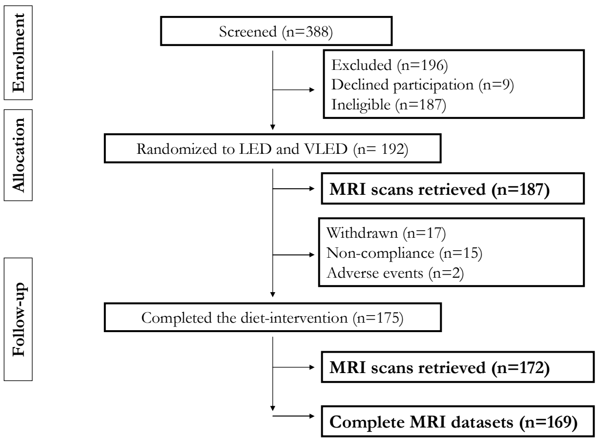
CLINICAL STUDIES

Study methodologies

Designs; Study I was a cross sectional study whereas studies II and III were based on longitudinal designs.

Participants; Patients for these studies were all participants in a study examining ´the influence of weight-loss or exercise on cartilage in obese knee OA patients´ (The CAROT trial) (ClinicalTrials.gov identifier: NCT00655941). In this trial, 388 possible subjects were pre-screened, 192 were enrolled and following the 16 week study period with an intensive diet-intervention, 175 patients still remained in the study (figure 3). Results in this thesis origin from the initial 16 week diet intervention, which was chosen as the knee joint was assumed to be maximally relieved at this time point (following an expected weight-loss in the magnitude of 10 % of the participants' initial body weight). Baseline and week 16 assessments included clinical examinations, MRI, CR, muscle strength tests, gait analyses, blood samples and collection of patient reported outcomes (PROs) with a variety of generic and specific health status questionnaires.

Figure 3. Trial profile for study I-III.



Eligibility criteria; Age ≥ 50 years; BMI ≥ 30 and primary KOA diagnosed according to the ACR criteria [57] with clinical symptoms as well as a verified diagnosis obtained from either radiographs or arthroscopy.

Patients were not included if any of the following criteria were present: lack of motivation for weight reduction; insufficient verbal understanding or intellect; planned anti-obesity operation (e.g. gastric bypass etc.); former or planned TKR; patients in pharmacologic treatment for obesity; medical disease that prevents physical training; active joint disease besides KOA; significant hip OA or toe or foot deformity which influences gait analysis; use of morfica or alike.

Interventions; The dietary intervention lasted 16 weeks and the first phase of the study consisted of an 8-week weight reduction programme where the participants were randomized to either an all-provided very low energy diet (VLED) with 415–554 kcal/day or a low energy diet (LED) with 810 kcal/day in a supervised dietary programme with weekly attendance at dieticians (products provided by The Cambridge Weight Plan). The patients attended weekly sessions of 1.5-2 h and were given nutritional and dietetic instructions by an experienced dietician. Daily intake of protein was at least 43.2 g (1.52 oz), and the intake of essential fatty acids, linoleic acid and linolenic acid was 3 g (0,11 oz) and 0.4 g (0.01 oz), respectively.
The second phase of the study, which was the same for all participants, consisted of 8 weeks' fixed energy diet programme using 1200 kcal incorporating two diet products daily. Participants continued to attend the groups to which they were initially allocated. All participants were taught to make diet plans with five to six small meals a day. The principles of the diet were in line with the guidelines for healthy eating issued by the Danish National Board of Health, i.e. low-fat, low-sugar and high-fibre. The focus was on long-term lifestyle modifications; educational themes were: energy expenditure and energy balance, macronutrients, satiety, digestion, motivation and diet planning. The group treatment provided a combination of empathy, social support and friendly competition. Further information about the weight loss program has been published elsewhere [168,169].

Imaging techniques

Radiographs; bi-plane weight-bearing non-fluoroscopic semi-flexed radiographs were taken at baseline of the target knee (most symptomatic); one in the posteroanterior and one in the lateral view (in case of bilateral symptoms we used the most symptomatic knee) using a Philips Optimus apparatus with a film-focus distance of 1.5 m. The same radiographers, using a standardized protocol, carried out all examinations [54].
MRI; High-field MRI recording was carried out using a 1.5 tesla (T) whole body scanner (Philips Intera, software release 12.1.5.0). Patients were positioned lying on their back, a receive-only flex medium or large coil was fixed to the patient's leg and a series of sequences were performed according to our MRI protocol (table 1).

Table 1. Pulse sequences performed with the 1.5 T MRI scanner.

Meta data	T1-FFE	PDw TSE	T2w TSE	T1 TSE	STIR
2D / 3D	3D	2D	2D	2D	2D
Plane	Sagittal	Sagittal	Sagittal	Coronal	Coronal
TE (milliseconds)	8.4	15.4	100	17	55
TR (milliseconds)	21	2531.3	2531.3	500	1797.9
TI (milliseconds)	-	-	-	-	160
Flip angle (°)	20	-	-	-	-
FOV (mm)	160 x 160	170 x 170	170 x 170	150 x 150	150 x 150
Matrix	512 x 512	256 x 256	256 x 256	512 x 512	512 x 512
Slice thickness (mm)	3	4	4	3	3
Gap thickness (mm)	-	10 %	10 %	10 %	10 %
Reconstruction	+	+	+	+	+
Acquisition matrix	256 x 256	256 x 201	256 x 201	301 x 243	256 x 201
Coil	Flex large	Flex large	Flex large	Flex large	Flex large

All image acquisitions were carried out at inclusion and after 16 weeks, scan time was approximately 35 minutes. In order to diminish bias of the results the same scanner were used at both time points.

Imaging assessments

Radiographs; the radiographs were analysed using an atlas as reference [56] and scored according to the KL grading system [55]. KL was chosen as it was estimated to be a widely accepted KOA score and probably the most commonly applied non-metric radiographic scoring within obesity research in KOA [28,105,169,170]. The three knee chambers (the medial and lateral tibiofemoral (TF) and the patellofemoral (PF)) were graded separately and a whole knee KL was computed as the maximum score in either chamber. The mJSW [171] assessments showed inter- and intra-reader results with intraclass correlation coefficients (ICCs) of 0.93 and 0.98 [88], respectively, which are comparable to the latest review on this topic [172].
MRI; MRI sequences were graded according to BLOKS as this scoring system was judged superior to other available scoring systems (KOSS and WORMS) in terms of having cartilage scores which were expected to provide a better comparison of semi-quantitative scores to volumetric data. Also, BLOKS encompasses scores for meniscus extrusion and sub scores for the location of BMLs in relation to the knee joint surface which could be important for future comparisons of MRI and gait-laboratory data within the CAROT-study. BLOKS variables were graded according to the description by Hunter et al. [61], including their online appendices, and assessed according to the description below. The BLOKS incorporates a region specific cartilage score I with two sub scores (overall loss and full thickness loss) and a point-specific cartilage score II. Cartilage assessments were performed using the

3D T1-fast field echo (FFE) sequence [121,173,174]. BMLs appear as ill-defined signal intensity changes in the subchondral bones that are hypointense on T1w images and hyperintense on Short T1 Inversion recovery (STIR) images [134]. All areas and all three subgrades (size / % BML, as distinct from cyst / % adjacent to subchondral plate) of the BML assessment were performed, however the imaging protocol did not allow for the assessment of BMLs in patella.

BMLs were scored using these two sequences, as evidence support that combining the two is highly effective for the evaluation of BMLs [118,175], even though some data suggests that T2 weighted (T2w) fat saturated (FS) sequences might be more sensitive [118]. BML assessments were done semi-quantitatively in 7 of the 9 regions of the knee as described in the BLOKS scoring system [61] as we discarded the BML assessments in the medial and lateral patellar region. Synovitis and effusion were evaluated on proton density weighted (PDw), T2w and STIR sequences [64] and the assessment of activity in Hoffa's fat pad was handled as a surrogate for whole-knee synovitis [61,141]. Osteophytes were evaluated using all three planes. In the axial plane we scored lateral and medial osteophytes on patella as well as anterior and posterior osteophytes on femur. In the coronal plane we assessed central weight-bearing osteophytes on tibia and femur. In the sagittal plane we examined the anterior and posterior osteophytes on femur and tibia, as well as the superior and inferior osteophytes on patella [61]. For evaluation of menisci we analysed morphology, tears and extrusion on the coronal T1w TSE (body) and on the sagittal T2w/PDw sequences (anterior and posterior horns) [176]. Abnormalities in the anterior and posterior cruciate ligaments were assesses using the sagittal T2w and PDw scans as recommended and previously performed [64,177]. In the analyses of MRI items we summed scores of individual assessments within each item to form a sum-score for each of the three compartments. Only for osteophytes, effusion and synovitis scores did we sum scores to form a whole joint score. Also, as others we did not include scores from the tibial intercondylar region.
All assessments of CR and MRI were performed using the MacOS X based Osirix software (v. 3.9.1) [178].

Anthropometrics
The following biometric values were measured: body weight (fasting when arriving in the morning) without large clothing and shoes to the nearest 0.1 kg on a decimal weighing scale (TANITA BW-800, Tanita Europe BV Hoogoorddreef 56e, 1101BE Amsterdam The Netherlands); height, using a stadiometer, rounding off the values to the nearest 0.5cm. From body mass and height, the BMI was calculated (kg/m2).

Patient reported outcomes
Symptom self-assessment was carried out at baseline and again at follow-up (t = 16 weeks), with assessments of the OMERACT-OARSI Responder Criteria and KOOS (see abbreviations) [179].
The OMERACT-OARSI responder criterion was assessed by visual analogue scale (VAS) pain, and function and patient global 0 to 100 mm scales [180].
The KOOS assessed impairment, disability and handicap with 42 items in 5 domains (function of daily living, pain, knee-related quality of life, symptoms, and function in sport/recreation). Items are scored from 0-4 and then transformed into a 0-100 scale; 0 representing extreme knee-related problems and 100 representing no knee-related problems [179].
OMERACT-OARSI was registered as primary outcome on www.clinicaltrials.gov (NCT00655941) for the CAROT-study and was chosen as such because it has been anticipated to be the simplest definition for measuring symptomatic improvements in clinical trials by the two largest academic organizations within OA [180].

Muscle strength
Isometric maximal voluntary contraction (MVC) of hamstrings and the quadriceps muscles were assessed by isometric dynamometry at 60° (0° is full extension) knee joint flexion angle (Biodex System 3 PRO, Biodex Medical System, NY, USA) as described [181]. After calibrating the system, the subject was comfortably seated and fastened to the dynamometer chair with leg- and body-straps. Prior to the measurements, a correction for gravity was made by registering the leg's weight at 0° knee joint angle. After test trials, performed to familiarize the patients to the test, the average peak value of three trials was chosen as MVC. Vigorous verbal encouragement was given in an attempt to achieve maximal effort level. Isometric MVC-values were normalized to body mass (Nm/kg) [182].

Knee joint alignment axis
The mechanical axis alignment was measured using a 6 camera stereophotogrammetric system (Vicon MX, Vicon, UK) with markers placed on anatomical landmarks (2nd metatarsal head, lateral malleolus, posterior aspect of calcaneus, lateral aspect of the leg, lateral femoral epicondyle, lateral aspect of the thigh, bilaterally on the superior anterior and posterior iliac spines) according to the Plug-in-Gait biomechanical model, and anthropometric measurements (height, leg length, and knee and ankle diameters) to determine joint centres. Investigators performing the gait analyses uncovered the superior posterior iliac spines in order to locate the patients' midline and the superior anterior iliac spines (SAIS) to measure the SAIS-distance. Placing of markers on SAIS was flawed due to patients' extreme obesity but with 3D computer correction this placing of markers on these important anatomical landmarks was optimized as much as possible. A similar approach was developed to correctly estimate the location of the lateral femoral epicondyles.
The mechanical axis alignment was defined as the frontal plane knee joint angle expressed in the local joint coordinate system. This procedure yields estimates of mechanical axis alignment similar to full-limb weight-bearing radiographs (R^2=0.54) but without exposure to radiation [183]. A knee was defined as a varus when alignment was >0º and valgus when <0º.

Statistics
In this thesis, several different approaches for the statistical analyses were chosen according to the study design and adapted to whether or not the data exhibited normal distribution or not. All the analyses were performed on SAS statistical, software versions 9.1 and 9.2 for Windows (SAS Institute Inc., Cary, NC, USA). A P-value less than 0.05 (two-tailed) or a 95 % confidence interval (CI) not including the null hypothesis was regarded as statistically significant.

Ethics
The trial protocol was submitted and approved by the local ethical committee of The Capital Region of Denmark before initiation (H-B-2007-088). Patients were carefully informed about the purposes of the trials, and their rights as participants were made

clear to them both verbally and in writing. Following this, all patients participating signed and approved the informed consent. The trials were carried out in accordance with the Helsinki Declaration II and the European Guidelines for Good Clinical Practise.
Concerns on imaging related primarily to CR, as the ionizing radiation dose per examination is estimated to be 0.006 mSv, corresponding to 0.2 % of the annual background radiation on earth. MRI provides no ionizing radiation but may be unpleasant for patients suffering from claustrophobia.

RESULTS

The CAROT-study included 192 obese KOA and following the 16 weeks diet intervention 175 (%) patients remained in the study. 187 (97 %) MRI scans were completed at baseline, 172 (98 %) MRI scans were obtained at week 16 and this left the study with 169 (97 %) complete MRI datasets (figure 3).

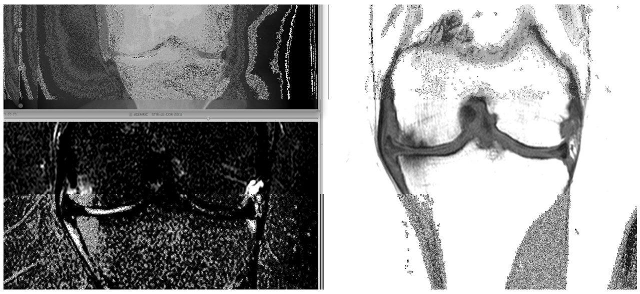
187 MRI scans were analysed in studies I and II and 169 MRI scans were analysed in study III (figure 3). No statistically significant differences were detected between baseline characteristics of all the initially included patients (n=192) and the 169 patients included in the analyses in study III (p<0.05).

The average KOA patient entering the trial was a 63 year old woman with a BMI of 37 having a symptomatic index of 60 on KOOS pain and function in daily living. This cohort displayed a wide variety of structural changes when assessed by MRI and CR. At baseline, the majority of the cohort had BMLs, displayed a mild to moderate degree of cartilage pathology and most patients had moderate to severe meniscal damage. The majority of patients exhibited a diminished mJSW, compared to non-KOA population, and was classified as having KL 2-3 [184-186].
19 patients had only medial TF KOA (medial KL ≥ 2 while the other compartments had KL scores ≤ 1), 7 patients merely had lateral TF KOA and 13 patients had solely PF KOA. Discarding the PF compartment, 53 patients had unicompartmental medial TF KOA (medial KL ≥ 2 and lateral KL ≤ 1) whereas only 12 patients had solely lateral TF KOA.

In the first study reliability assessments of BLOKS were carried out by scoring 20 MRI examinations of executively selected patients from the baseline MRI examinations. Selection was performed according to a pre-established protocol, so that the analyses were completed on ten females and males, respectively. The chosen cases represented all levels of KOA joint damage, evaluated by the medial compartment KL (2 patients having KL grade 0, 6 patients having KL 1, 4 patients having KL 2, 6 patients having KL 3, and 2 patients having KL 4) [61]. Analysis showed inter-reader results between 0.51-0.80 and intra-reader results between 0.58-0.90 (kappa-values).

The comparison of imaging modalities revealed that the compartmental KL had the highest level of association with ipsilateral MRI assessed joint pathology, in particular in the medial TF compartment, and the mJSW had a strong correlation to BLOKS items (see figure 4).

Figure 4. Comparison of CR and MRI.



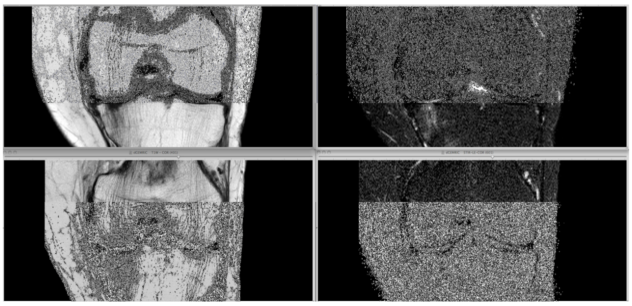
Coronal STIR (left), coronal T1w (right) and a PA radiograph

The three KL gradings were moderately to highly correlated to cartilage damage (r=0.43 to 0.76) with a tendency towards higher associations observed to cartilage score I compared to cartilage score II.
The medial KL had a moderate correlation to BMLs and meniscus pathology in the medial TF compartment (r=0.57 to 0.68) whereas the association between the lateral KL and the ipsilateral gradings of BMLs and meniscus pathology (r=0.15 to 0.30) were weak. mJSW correlated to cartilage scores (r=-0.14 to -0.70) and was associated to synovitis, effusion as well as medial BMLs and meniscus pathology. The two radiographic scoring systems (KL and mJSW) showed a statistically significant negative correlation (r=-0.32 to -0.73).
Analyses of the compartment-specific KL grade gave an indirect reflection of the MRI based assessment of knee joint pathology. Noticeable in this context was that pathological damage in both cartilage and menisci was present even for radiographically assessed mild KOA (KL 0-1). Tissue damage evolved markedly with RKOA deterioration and this was in particular noticeable for scores of cartilage and menisci scores (p<0.0001).
In the second study we examined whether or not baseline measurements of joint damage, assessed by MRI and CR, or general knee malfunctioning, assessed by knee joint alignment and muscle strength, could predict the symptomatic outcome following the 16 weeks diet intervention. The effect of this diet intervention was a median improvement in symptoms from baseline to week 16 of 14.0 % (KOOS pain) and 15.8 % (KOOS function in daily living). Patients lost on average 12.5 % of their body weight (SD 5.6). The analysis did not reveal any significant correlation between symptomatic improvement and the chosen predictors (Δ ADL and Pain, r ≤ 0.13; p > 0.05) except for the effusion score and Δ ADL (r 0.17, p = 0.03). Analysing the predictive effect of baseline measures on structural damage on the OMERACT-OARSI Responder Criterion, we found that neither of our included explanatory variables showed any statistically significant impact (p > 0.07). The study also examined the reliability of mJSW, which showed ICCs for the inter- and intra-reader analyses were between 0.93-0.98, respectively.
In the final study we examined the influence of diet intervention on changes in the total amount of BMLs as well as in the maximum BML scores. 39 patients (23 %) experienced a decrease in the sum of all BML size scores (responders) (figure 5a, b and c) and 130 patients (77 %) deteriorated in their score or remained stable (non-responders) (figure 6).

Figure 5a. Example of BML size improvement from baseline (top slices) to week 16 (bottom slices).

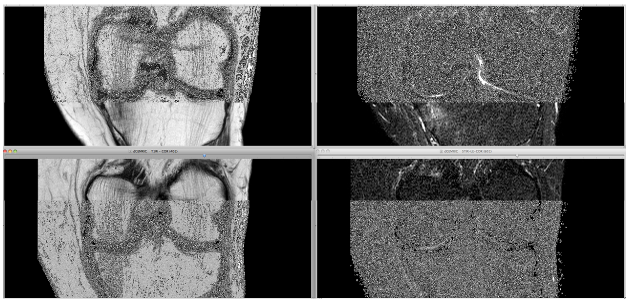
Coronal STIR sequence (left) and coronal T1w sequence (right)

Figure 5b. Example of BML size improvement from baseline (top slices) to week 16 (bottom slices).



Coronal T1w sequence (left) and coronal STIR sequence (right)

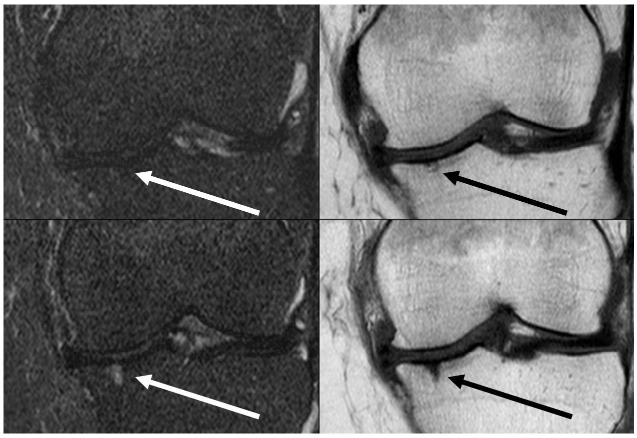
Figure 5c. Example of BML size improvement from baseline (top slices) to week 16 (bottom slices).



Coronal T1w sequence (left) and coronal STIR sequence (right)

Logistic regression analyses revealed no association between weight loss category and response in BML size in the most affected compartment (OR =1.95 [CI 0.70 to 5.45, p=0.20]). Adjusting for age, gender and randomization group did not change the results significantly (OR 1.86 [CI 0.66 to 5.26, p=0.24]).
There were no association between weight loss during and response in maximum BML score (OR 1.13, CI 0.39 to 3.28, p=0.81). There were no differences in BML responses in the underlying RCT (VLED and LED diet interventions) (data not shown).

Figure 6. An example of BML size deterioration from baseline (top slices) to week 16 (bottom slices)



Coronal STIR sequence (left) and coronal T1w sequence (right)

The relationship between changes in BMLs and clinical symptoms revealed that an equal percentage of patients classified as BML responders and non-responders experienced an OMERACT-OARSI response (69 vs. 71 %, p=0.86). KOOS pain improved 23.9 and 22.6 % for BML responders and non-responders, respectively (mean difference 1.3 [95% CI -14.3 to 11.7], p=0.84) and similar results were found for KOOS ADL (25.6 and 25.7 %, mean difference 0.1 [95% CI -14.2 to 14.3], p=0.99).
Comparable results were found when analysing the association between response in maximum BMLs and KOOS pain (16.3 and 24.2 %, mean difference -7.9 [95% CI -6.8 to 22.6], p=0.29) as well as KOOS ADL (20.5 and 26.7 %, mean difference -6.2 [95% CI -10.0 to 22.3], p=0.45).
Examining whether or not patients with the highest symptomatic improvements or weight loss´ had an increased chance for improving their BML scores (total or maximum scores) revealed that there were no statistically significant differences between the highest and lowest quartiles (p<0.05).

DISCUSSION AND CONCLUSION

Obesity is a modifiable feature in KOA pathogenesis and examining the effect of diet intervention in KOA research is therefore very important.
In this thesis we aimed to perform reliable imaging assessments in order for us to examine if obese patients are to be recommended weight loss as a treatment for KOA symptoms, despite their level of knee joint damage and malfunctioning, as well as to investigate the effect of weight loss on BMLs.
The incidence of obesity has gradually increased over the past decades. Since subjects become susceptible to KOA with increasing age [21] and overweight [23], KOA is expected to become a major disabling disease in the future [14]. Evidence suggests that normal knee function is particularly important for elderly citizens, and that the influence of musculoskeletal disease leads to loss of physical function and dependency on health care [16-18]. This in turn may lead to inactivity and thereby an increased morbidity

and mortality [15]. Also, clinical symptoms of KOA are increased in obese individuals and it is known that weight-loss can both improve symptoms [28] and decrease the risk of KOA development [24,25]. A major weight reduction has been shown to significantly improve the KOA related symptoms [86] regardless of the severity of structural KOA changes seen on MRI [87,88].

This thesis contains reliability analyses of BLOKS and mJSW which were comparable to those found in the original study defining BLOKS [61,187] and to those reported in the latest review focusing on the reliability of mJSW measurements [172]. Focusing on BLOKS, results from the gradings of cartilage damage revealed that our cohort was scored as expected by the schematic layout by Lynch et al [128] and this strengthens the impression of our capability to analyse MRI scans by BLOKS.

All together, these findings imply that different MRI investigators can apply this complex scoring system and obtain reliable results and this remains crucial for future comparisons of results between separate research groups.

This thesis confirmed a close association between radiographic and MRI based assessments of knee joint structures and added important details to our knowledge of joint damage in obese elderly KOA patients. For patients displaying minimal damage on radiographs our study showed that they already had important pathological changes in a variety of joint tissues, including bones, cartilage and menisci, with a steep rise in the extent of pathologic damage at TF KL grades of 2-3.

This confirms in some ways the consideration that as joint homeostasis is put off balance the overall joint stress increases, and this leads to structural failure [7] with the development of definite KOA compromising both cartilage, bone marrow, ligaments, menisci, and joint capsule [2,7,19,20]. The compartmental analyses of ipsi- and contralateral correlations of MRI and CR based scorings revealed that compartment specific KL scores correlated more significantly to ipsilateral MRI scores. Altogether, the comparison of imaging modalities indicates that CR assessments are useful and informative on a cross-sectional basis, that a compartmental analysis strategy reveals differences in the association between MRI and CR and indicate that important information may be gained by performing MRI scans.

Although KOA is known to be a phenotypically heterogeneous condition [10], the present thesis reveals that diet intervention for the treatment of KOA symptoms is recommendable for obese patients. Study II demonstrated that baseline structural damage assessed by imaging, mechanical axis or muscle strength did not predict the symptomatic outcome of a 16 week diet intervention in this group of elderly female obese KOA patients. To the best of our knowledge this is the first study to demonstrate that the presence of KOA related structural joint damage, examined by a series of different methods, did not preclude a symptomatic improvement following a significant weight loss. In this study the majority of patients obtained a significant weight reduction (> 10 %), and 64 % of the patients experienced a significant symptomatic improvement defined by the OMERACT-OARSI responder criterion. The results are consistent with prior studies investigating short-term effects of weight-loss and long-term outcome of total knee joint replacement [27,86,188,189]. Even so, it is important to acknowledge that weight loss is hard to achieve for overweight and obese elderly individuals with limited mobility and adhering to a weight loss scheme is difficult.

Identifying sub-groups of KOA patients who have an increased chance for successful response to diet intervention may improve the effects of dieting-programs. As such, examining predictors of effects following diet intervention in KOA is highly relevant in the planning and conduction of clinical trials. A number of other studies have examined baseline characteristics as predictors of effects of studies exploring other types of interventions, all aiming at relieving the symptoms of KOA [190,191]. A recent study, testing predictors of effects of a patient-tailored conservative treatment regime, reported results comparable to what was seen in study II [82]. However, the heterogeneity of this cohort decreased the ability to find such important associations.

KOA is a progressive disease with worsening of both clinical symptoms [18] and structural damage [147-149,152] over time. BMLs are the MRI feature most strongly related to the future degeneration of the joint in KOA [192,193] as well as prevalent clinical symptoms [68]. The results of study III showing that weight-loss did not improve the overall or maximum BML scores, is an important discovery, despite the fact that our results were not associated to the short-term effect on clinical symptoms.

Prior to the intervention our cohort had a high prevalence of BMLs, which is somewhat in contrast to previous reports investigating symptomatic KOA patients [135,136]. Previous data have reported that BMLs fluctuate over time. The development in BML size scores in study III was comparable to results from the MOST study [194] and other studies [139,195], while BMLs in general developed more positive in our cohort when compared to data from other prospective observational cohorts [135,136].

The differences might be due to the very rapid and successful weight loss used in our study [169], which was applicable with high intensity with few adverse effects [168,196]. The present study did not provide any biological explanation for the response in BMLs. Existing literature suggest that obesity related inflammatory mechanisms [3,197] and biomechanical malfunction are related to structural damage [198] in the knee, but even so, the aetiopathogenesis of BMLs is still not fully understood. Missing the link between symptoms and BMLs in this longitudinal study may be due to the fact that assessments of clinical symptoms is a difficult task, as these self-reported outcomes are affected by more than just MRI assessed pathological changes [80,81].

In conclusion, this thesis supports existing guidelines recommending diet intervention for obese KOA patients. The thesis specifically adds the following new to the field of KOA:

1) Positive changes in patient reported outcomes are possible for the majority of obese, elderly KOA patients subjected to an intensive diet intervention program, whatever their general pre-study patient characteristics, level of structural damage and measures of muscle strength and malalignment may be. As such, bad knees are no excuse for not losing weight.

2) Achieving a rapid major weight-loss (>10%) did not show any relationship to changes in the sum of all BML scores in the TF compartments or the maximum BML score in the most affected knee joint compartment. Also, changes in KOA related symptoms and the above mentioned BML scores, following a 16 week diet intervention, were not associated.

STRENGTHS AND LIMITATIONS

Among the strengths of this thesis is the large patient cohort as well as the performed reliability analyses which were performed to ensure our capability to assess MRI with BLOKS. We show similar reliability in grading BLOKS compared to the original work behind the grading system, and results from the cartilage grading support that our KOA cohort was graded as expected from theory and that the segregation of gradings lye within the theoretical grading displayed in the schematic layout by Lynch et al [128]. In addition, we applied recognized radiographic scoring systems

[54,55,199] in all the studies and performed reliability analyses for the measurement of mJSW [88].

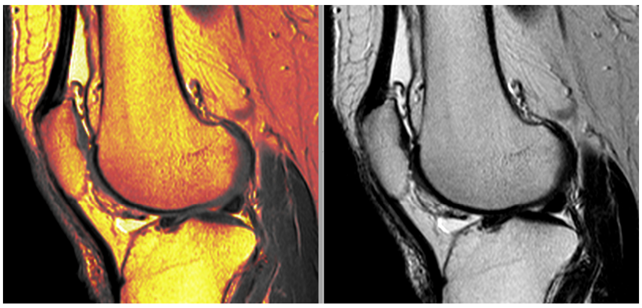
However, findings and conclusions in these studies have a number of limitations.
The external validity of the presented results may be limited to symptomatic KOA in secondary care and results are only representative for patients who are elderly and very obese. Even so, results from other trials does not suggest that findings should be less encouraging in obese KOA patients who are dissimilar with respect to patient characteristics for gender, age and BMI [28,170,200]. This thesis has limitations concerning the MRI protocol. First of all, at the time of study start, BLOKS was estimated to be the most suited scoring system for the purpose of the different studies undertaken within the CAROT-trial (see methods). Since the completion of our BLOKS assessments, the MOAKS was introduced, which provide some advantages for longitudinal studies [62]. One advantage of WORMS could be its, in general, regional approach whereas the BLOKS has a more lesion-based methodology. In spite of these considerations, no study has yet directly compared the existing systems (KOSS, WORMS, BLOKS and MOAKS) nor shown results that support one system over the others [128,201,202]. Factual advantage of one scoring system can probably not be established.

In general, limitations were that our analyses were based on assessments from a single MRI examination and that we did not assess between scan reliability.
These factors could potentially result in erroneous estimations of associations due to varying patient positioning and to the observed variability of some structures. The MRI protocol for this study did not include all the recommended sequences for optimal gradings of all possible MRI features of KOA pathology. However, we believe that the BLOKS assessment performed served the question addressed in this thesis. Learning from our experiences we would, however, have chosen to add at least two additional sagittal scans (STIR and T1) and preferably also fat saturated T2 or PD sequences in three planes. The protocol included one plane MRI scans for the evaluation of BLOKS BMLs, and even though a single plane assessment seems reasonable [128,203], it is likely not to be optimal. In general, we consider the coronal STIR and T1w sequences adequate for a reasonable assessment of BMLs in the tibial and femoral bones as Osirix allowed for a localization of the scored lesions by using sagittal sequences obtained for other purposes. However, we recognize the limitations this strategy withholds in terms of correctly assessing BMLs located at the margins of our slices when only having coronal slices in our MRI protocol. Due to an inadequate coverage of we did not analyse BMLs in patella (see figure 7) which confined the thesis to only study changes in the tibial and femoral bones.

Figure 7. Coverage of coronal MRI scans.

The chosen sequence for cartilage assessment has been compared to the newer sagittal 3D DESS WE sequence on 3 T scanners, and despite the fact that the latter seemed to be more reproducible, our sequence seems very reliable for the assessment of cartilage [204]. BLOKS contains separate scores for effusion and synovitis and we have assessed all MRI scans according to this discrimination well knowing that this procedure is biased and that a recent paper describing the MOAKS has proposed the combination of the two scores [62]. MRI technology allows for an excellent discrimination and delineation of synovitis and synovial effusion by performing MRI with I.V. gadolinium and post-contrast T1 FS images [62,205-207], but due to extensive requirements and longer scans times for such examinations we proceeded with our, in this matter, suboptimal MRI protocol. Nevertheless, by doing so, our findings are directly comparable with the majority of available literature on synovitis/effusion in KOA. As such, our assessment was performed as a mere presence or absence of synovitis at the listed sites described in the BLOKS web-only appendix. As a supplement to the usual assessment we also used a non-validated fusion function in OSIRIX enabling a possible enhanced view between the potential effusion and synovial hypertrophy in the sagittal plane (see figure 8).

Figure 8. Image example of a MRI image fusion performed in Osirix.



As other researchers we chose to sum the scores of individual assessments of cartilage pathology, BMLs and menisci to form a sum-score for each of the three compartments and to exclude scores from the tibial intercondylar region [208-212]. The intercondylar area was excluded as this approach is common within KOA research and might provide an advantage when comparing BMLs to other MRI items within either knee compartment. Scores were summed because it indeed seems interesting and relevant to examine how the "total" amount of specific pathological findings on MRI is related to radiographic measurements. In our

opinion, this is specifically important for an obese cohort as ours, as the aetiopathogenesis behind KOA in this part of the KOA population seems multifaceted [213].
Besides these specific considerations one should bear in mind that the apparent variety of sequences used for scoring MRI scans and the amount of different researchers involved within this field of KOA research weakens the ability to directly compare results between different trials and papers.

The existing literature on the appropriateness of the lateral view and/or the skyline view in knee radiographs describes that the optimal assessment of KOA would be achieved by performing all three radiographic views, but for this study we chose a radiographic protocol which was somewhat similar to the routine examination for KOA applied on a daily basis at our Department of Radiology [102]. Despite the fact that the skyline view would be preferential to the lateral view we proceeded with our protocol as the assessment of the PF joint is crucial for correctly diagnosing patients with KOA [185]. Research supports that the skyline view is superior to the lateral view if one aims to reproduce the PF JSW whereas an assessment of this joint using the lateral view must rely on atlas examples [214,215]. Considering the relationship of KOA pathology on radiographs with MRI detected cartilage damage, research has shown that cartilage volume correlates stronger to PF JSW on skyline views when compared to PF JSW on lateral views [216]. Even so, others have found that the sensitivity and specificity for detecting MRI verified cartilage damage in the PF compartment were identical for osteophytes assessed by either axial or lateral radiographs and that osteophytes in the PF joint correlates even better to cartilage damage than does other RKOA features (JSN and sclerosis) [217,218]. In terms of diagnosing PF KOA, verified by an operative classification (Outerbridge), a paper from Bhattacharaya et al found that the skyline view had a sensitivity of 79 % and a specificity of 80 %, similar results for the lateral view was 82 % and 65 %, respectively [219].
The three knee compartments (the medial and lateral TF and the PF) were graded separately. As the original grading by the KL system did not develop any standards for the assessment of the PF compartment we applied the KL criteria of the TF compartments to the PF compartment as an explorative marker in a whole joint radiographic assessment. Inspiration to do so was found in the paper by Felson et al as well as Hart and Spector [215,220]; an approach that has been applied by others [219,221]. This approach is supported by Chaisson et al who found that a PA view supplemented with either a lateral or skyline view resulted in a near identical level of sensitivity in the diagnosis of KOA [102]. In this sense it seems reasonable to assume that the combination of a PA and a lateral is excellent for diagnosing RKOA and that the lateral and skyline views perform nearly equally in terms of diagnosing cartilage damage in the PF joint.
A further limitation was that manual mJSW measurements were used for the assessment of JSN as we did not have access to a potentially superior computer-software for semiautomatic measurements [222].

In conclusion, our radiographic protocol could have been improved by including all three views of the knee joint as this would have allowed for a superior and more specific assessment as well as scoring of the knee.
In terms of measuring the knee joint alignment these measurements were influence by the fact that data on the axis were extracted from gait-analyses and that the included patients had so much body fat that placing the markers correctly was complicated. Even so, the scientist behind these analyses evolved a standardized procedure for performing the gait-analyses best possible.

FUTURE DIRECTIONS

The sustainability of the results from study II is still unknown, but as the CAROT-trial is an on-going study, our group has the opportunity to examine this subject in future studies. Furthermore, the hypothesis that ´obese knee osteoarthritis patients can achieve symptomatic improvements following diet intervention regardless their pre-study characteristics´ could be expanded with the inclusion of other relevant predictors.

Future studies are also to look into the effects of diet intervention and substantial weight-loss (>10 %) on KOA patients in relation to the long-term symptomatic outcome and development of imaging-assessed pathology. The effects seen on clinical symptoms [28,86,169] following diet intervention are well established [83] and future studies will aim to describe the benefits of diet intervention on a combination of several measurements and assessments of symptoms like, MRI, radiographs, gait lab analyses, biomarker assessments and PROs [1-6]. Specifically, trials examining the effects of diet intervention will incorporate measurements of cytokines [29,51], biomarkers such as S-COMP and U-CTX-II [1] and biomechanical properties [5,42,43,223]. With a broader spectrum of assessment methods, more can be learned about the complex interaction between joint loadings, cytokines and cartilage damage in relation to KOA symptoms and overall knee joint pathology [50,52].

Focusing on MRI, the CAROT-trial cohort withholds a unique opportunity to assess and compare damage on a series of joint structures) [61], cartilage quality (dGEMRIC) (figure 9) [119,127] as well as cartilage volume, thickness, curvature changes and homogeneity (figure 10-11) [117,120,122,131].

Figure 9. Case example of dGEMRIC analyses in the CAROT-trial.

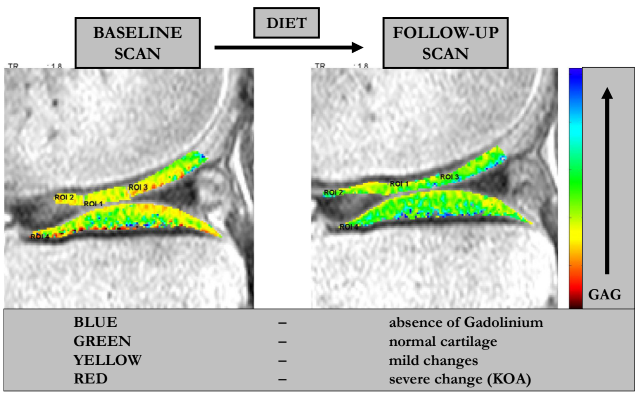


Figure 10. Segmentation of cartilage (by courtesy of Erik Dam, BiomedIQ).

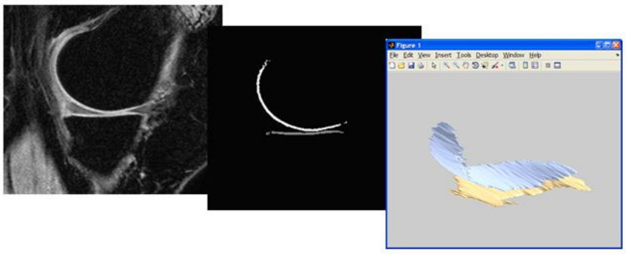
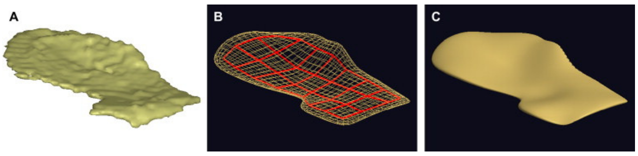


Figure 11. Surface visualization of a volumetric cartilage assessment (by courtesy of Erik Dam, BiomedIQ).



Future studies on data from the CAROT-trial will include measurements of GAG content in cartilage (dGEMRIC) as well as qMRI measurements, and these data will be compared to the immediate and long-term clinical outcome of weight-loss. In theory the patients' knee joint is expected to be maximally relieved following the 16 weeks of diet intervention, and examining the short-term effects of diet intervention on MRI-assessed structures is more likely to be detected by dGEMRIC and qMRI, compared to traditional MRI.

SUMMARY

This thesis examines two main hypotheses; 1. Obese knee osteoarthritis (KOA) patients can achieve symptomatic improvements following diet intervention regardless of their level of structural damage and overall joint malfunctioning 2. Rapid weight-loss in obese patients with KOA will lead to improvements in KOA related pathology that can be assessed and evaluated by MRI.

Data for the studies were obtained from obese KOA patients who were recruited for a 16 week diet intervention trial, the CAROT-trial (ClinicalTrials.gov identification no.: NCT00655941). Inclusion criteria were age ≥50 years, BMI ≥30 kg/m2 plus symptomatic and verified KOA. Patients underwent a 16 weeks dietary programme with formula products and counselling. Baseline and week 16 assessments included clinical examinations, MRI and CR of the most symptomatic knee, muscle strength tests, gait analyses, blood samples and collection of patient-reported outcomes with a variety of generic and specific health status questionnaires. MRI scans were graded by the BLOKS and CR was analysed by measuring the mJSW and grading the knee as described by KL. 388 possible subjects were pre-screened, 192 were enrolled. Following the 16 weeks diet intervention 175 (%) patients remained in the study. 187 (97 %) MRI scans were completed at baseline, 172 (98 %) MRI scans obtained at week 16 and this left the study with 169 (97 %) patients with complete MRI datasets at week 16. No statistical significant differences were detected between baseline characteristics of all the initially included patients (n=192) and the 169 patients included in the per protocol analyses performed in study III ($p<0.05$).

In order to apply BLOKS, an extensive MRI scoring system, in study II and III we examined the inter- and intra-observer reliability of the various BLOKS items in study I. Results showed that our assessment team performed as described in the original study defining BLOKS and that the patients in the CAROT-trial were graded as expected.
In study II we investigated the impact of diet intervention on KOA symptoms whatever the patient's individual level of joint damage and malfunctioning, and the explanatory variables included high-field MRI, radiographs, and muscle strength in m. quadriceps as well as measurements of the knee-joint alignment axis. Results showed that diet intervention resulted in a symptomatic relief in obese KOA patients, irrespective of their level of structural damage, measures of joint malfunctioning and general pre-study patient characteristics.
The final study examined whether or not weight-loss had an immediate impact on MRI assessed BMLs. The results showed that changes seen in the total TF sum of BML scores and maximal BML scores did not differ between patients achieving a major weight loss (> 10%) and those who did not. Furthermore, changes in clinical symptoms and BML scores were not associated.

The limitations of this thesis were that the MRI analyses were based on single determinations of MRI variables and that the studies did not assess between scan reliability. The MRI protocol for this study did not include all the recommended sequences for BLOKS. Analysing BMLs with the use of only coronal STIR and T1w sequences is considered adequate for a reasonable assessment of the tibial and femoral bones. However, we recognize the limitations this strategy withholds in terms of correctly assessing BMLs located at the margins of our slices when only having a single plane view included in our MRI protocol. Due to an inadequate coverage we did not analyse BMLs in patella, and this confined the thesis to only study changes in the tibial and femoral bones. BLOKS contains separate scores for effusion and synovitis and we have assessed all MRI scans according to this discrimination well knowing that this procedure is biased and that a recent paper has proposed the combination of the two scores. MRI technology allows for an excellent discrimination and delineation of synovitis and synovial effusion by performing MRI with I.V. gadolinium and post-contrast T1 FS images, but due to extensive requirements and longer scans times for such examinations we proceeded with our, in this matter, suboptimal MRI protocol. The optimal assessment of KOA would be achieved by performing three radiographic views, posteroanterior, lateral and skyline, but for this study we chose a radiographic protocol only including the first two mentioned as this procedure was somewhat similar to the routine examination for KOA applied on a daily basis at our Department of Radiology.

The results of this thesis support existing guidelines suggesting that diet intervention in obese KOA patients is beneficial for symptomatic improvements. The new information from the thesis is that improvement in clinical symptoms is possible for the majority of patients, independent of their pre-study level of structural damage and measures of joint malfunctioning. The present results also demonstrated that a rapid weight-loss had no association to changes in BML scores and established that changes observed in symptoms and BML scores, following a 16 weeks diet intervention, were not related

ABBREVIATIONS

ACR American College of Rheumatology
BLOKS Boston-Leeds Osteoarthritis of the Knee Score
BMI Body mass index
BML Bone Marrow oedema like Lesion
CAROT The influence of weight-loss or exercise on Cartilage in obese knee OA patients
CI 95 % Confidence interval
CNR Contrast to noise ratio
COX-2 Cyclooxygenase-2
CR Conventional radiography
dGEMRIC Delayed Gadolinium Enhanced MRI of the Cartilage
DMOADs Disease-Modifying OsteoArthritis Drugs
EULAR European League against Rheumatism
FFE Fast field echo
FOV Field of view
FS Fat saturated
GAG Glycosaminoglycans
GRE Gradient echo
ICC intraclass correlation coefficient
JSN Joint Space Narrowing
KAM Knee adduction moment
KL Kellgren & Lawrence
KOOS Knee injury and Osteoarthritis Outcome Score
KOSS Knee Osteoarthritis Scoring System
KOA Knee Osteoarthritis
LED Low energy diet
mJSW Minimum Joint Space Width
MOAKS MRI Osteoarthritis Knee Score
MRI Magnetic Resonance Imaging
MVC Isometric maximal voluntary contraction
NSAIDs Non-steroidal anti-inflammatory drugs
OMERACT-OARSI responder Criterion A tool developed by the EULAR/ACR group to assess the impact of an intervention in terms of evaluating improvements in clinical symptoms
PA Postero-anterior
PD Proton density
PF Patellofemoral
PRO Patient reported outcome
qMRI Quantitative MRI, referred to when measuring cartilage volume and/or thickness
RKOA Radiographic KOA
SD Standard Deviation
SE Spin echo
SNR Signal to noise ratio
STIR Short TI Inversion Recovery
T Tesla
TE Echo time
TF Tibiofemoral
TI Inversion time
TKR Total Knee joint Replacement
TR Repetition time
TSE Turbo spin echo
AS Visual analogue scale
VLED Very low energy diet
WORMS Whole-Organ Magnetic Resonance Imaging Score

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