Unloading therapy for medial knee osteoarthritis

Clinical outcomes and quantitative imaging considerations

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Colophon

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Unloading Therapy for Medial Knee Osteoarthritis:
Clinical outcomes and quantitative imaging considerations

Valgiserende therapie voor mediale knieartrose:
Klinische resultaten en overwegingen omtrent kwantitatieve beeldvorming

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Clinical outcomes

Quantitative imaging considerations

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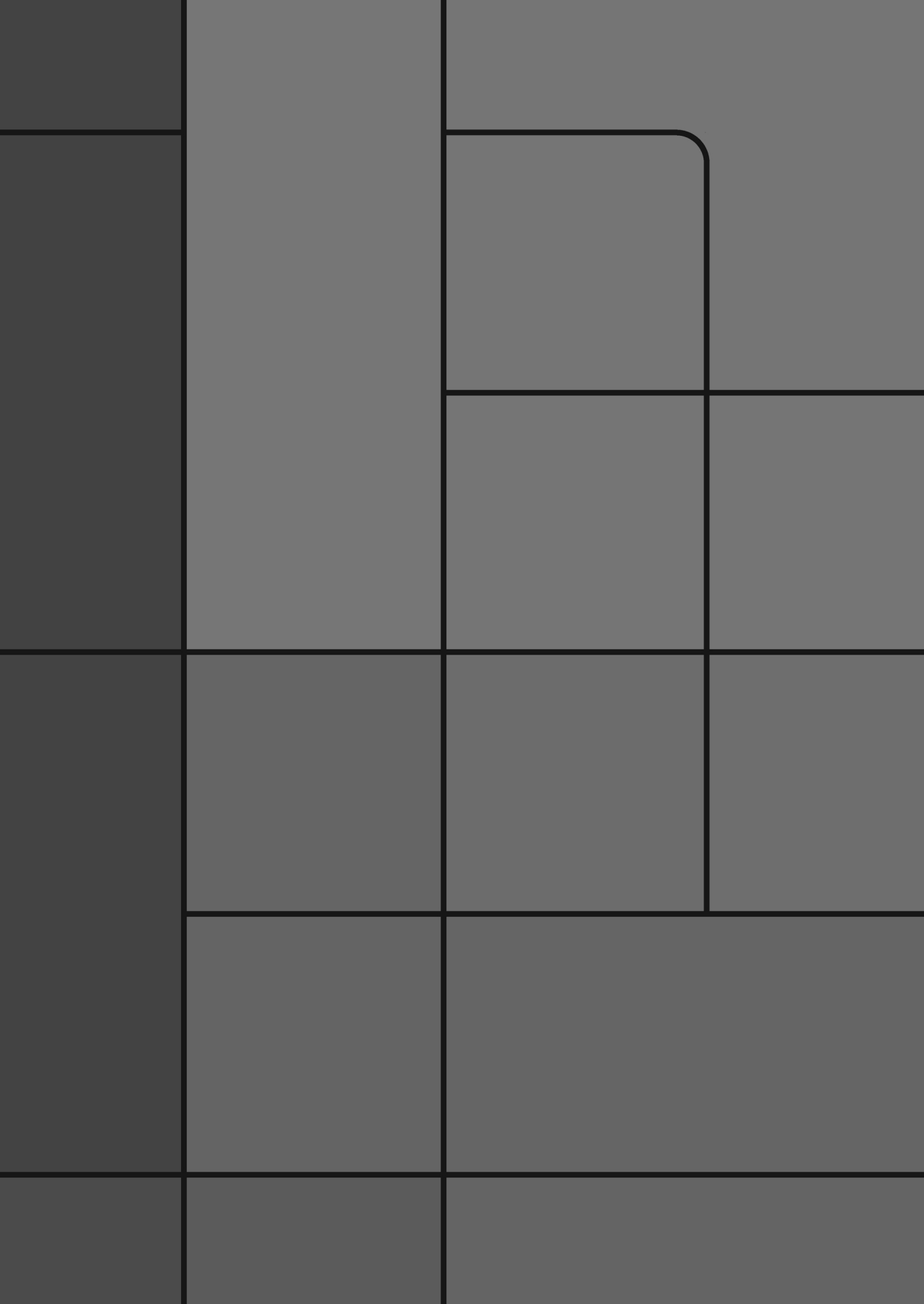


Chapter 1

General introduction

Knee osteoarthritis

Osteoarthritis is a joint disease characterized by the degeneration of tissues.[1] A key feature is the degeneration of the hyaline articular cartilage. This articular cartilage covers the bone ends that form the joint. A composition of collagen, glycosaminoglycans (GAGs), chondrocytes and water create a resilient tissue with a smooth surface, ideal for the articulation.[2] As the cartilage deteriorates, it becomes thinner and of poorer quality. However, it has long been known that not only the cartilage deteriorates. Also other tissues of the joint show degeneration, such as the subchondral bone, joint capsule, menisci and ligaments (Figure 1).[3] Although the development of osteoarthritis has a strong association with age and BMI, it is not just the result of mechanical wear.[4, 5] Osteoarthritis has a multifactorial cause, which involves mechanical, inflammatory, genetic, and metabolic factors.[6-8] The general deterioration of the joint leads to a painful joint that can be stiff and may have a reduced range of motion. Other symptoms include swelling, instability and malalignment of the joint.

Osteoarthritis is the most common joint disease leading to disability worldwide.[9] Women are more often diagnosed with osteoarthritis than men. Of all the joints, the knee is most symptomatically affected. According to the Global Burden of Disease study, knee osteoarthritis accounts for roughly 85% of the burden of osteoarthritis worldwide.[10] The total number of patients diagnosed with osteoarthritis in the Netherlands is estimated at 1.5 million on a population of 17.5 million. Half of these patients have knee osteoarthritis. According to the Dutch National Institute for Public Health and the Environment, 43,700 patients were diagnosed with knee osteoarthritis in 2021.[11] Although these are already considerable numbers, several studies have shown that these official figures underestimate the true number of people diagnosed with knee osteoarthritis. The actual number is probably two times higher.[12] The aging population and increasing obesity lead to an increasing prevalence of knee osteoarthritis. The enormous prevalence of osteoarthritis has a major impact on the healthcare expenditures, which were estimated to be 1.1 billion euro in the Netherlands on a healthcare budget of around 81 billion euros in 2019.[13] The indirect costs caused by not being able to work and premature retirements are not included in this calculation.[14, 15] The total cost in western countries are estimates to be 1-2,5 percent of the gross domestic product.[1, 16] The large burden of the knee osteoarthritis warrants the research on more accurate diagnostic imaging tools and new disease modifying treatments for the disease.

The knee is a hinge joint consisting of the femorotibial and the patellofemoral joint. It is divided into a medial and lateral femorotibial compartment and a patellofemoral compartment. Because the knee allows translational and rotational movement in all the anatomical planes and axes (coronal, sagittal and transverse) the function of the knee is very complex. The fact that the knee is most susceptible to osteoarthritis is due to the complex functioning, the great forces it is exposed to and the susceptibility to traumatic injuries, such as ligament injuries, meniscus injuries and traumatic cartilage injuries.[4] It has been

demonstrated that these injuries accelerate osteoarthritis development.[17-19] Although knee osteoarthritis can develop evenly throughout the joint, it generally predominates in one of the knee compartments with the medial femorotibial compartment most often affected.[20-25] In a knee with normal alignment, about 62-75 percent of the load is transferred through the medial compartment.[26-30] When there is a varus knee malalignment, the transmission of forces will lean even more towards the medial compartment, making it a risk factor for the development of osteoarthritis (Figure 2).[22, 24, 31-34] This makes knee malalignment a highly potential target for interventions.[35]

Treatment

The treatment of knee osteoarthritis depends on the stage of the disease. Current treatment for patients with mild complaints is with conservative measures, such as education, lifestyle changes, weight loss, exercise therapy and pain medication.[36-41] At the other end of the spectrum, when there is end-stage osteoarthritis, the knee can be constantly irritated and the patient's quality of life is greatly reduced because of the complaints.[1, 42, 43] For these situations, there could be an indication for joint replacement therapy such as unicompartimental or total knee arthroplasty. In knee arthroplasty, the worn out cartilage is removed and the distal femur and proximal tibia are cut to size to accommodate metal components. Knee arthroplasty can effectively reduce pain and function impairment.[44-47] However, the function of an artificial knee will never be as good as a native knee. Certain movements such as kneeling down are generally not tolerated. It is also a major surgical procedure with an extensive rehabilitation period and some serious risks involved.[48, 49] We also know that up to 25 percent of the patients treated with knee arthroplasty are not satisfied. While pinpointing a definitive cause for dissatisfaction among most patients can be challenging, unrealistically high expectations likely play a significant role.[50] The proportion of less satisfied patients appears to be greater in younger patients and patients without end-stage osteoarthritis.[51-53] Finally, younger patients have a far greater life time risk of requiring revision surgery and the median time to revision is shorter than in older patients.[54, 55] Therefore, arthroplasty should be reserved for patients with advanced stage osteoarthritis who do not respond to conservative or less invasive therapies.

For patients with moderate medial knee osteoarthritis and a varus knee malalignment, an unloading therapy is a logical procedure.[35] By unloading the medial knee compartment, stress is relieved from the affected area and is shifted towards the less osteoarthritic or even healthy lateral compartment. Herewith, symptoms can be reduced and disease progression can be delayed. Among the available unloading treatments, a valgus unloader brace is an important conservative therapy, while high tibial osteotomy (HTO) is the primary operative treatment (Figure 3). The unloader brace applies an external valgus stress to the knee. With an HTO the varus knee malalignment is surgically adjusted to a neutral or slight valgus knee alignment by creating or removing a wedge in proximal tibia to change the angle

between the tibial plateau and the tibia shaft. The osteotomy is fixed using a metal plate and screws or with metal staples. Both are well-established therapies with their own advantages and disadvantages. An unloading brace can be started easily, is non-invasive, relatively inexpensive and does not require a rehabilitation period. On the other hand, in order to achieve adequate valgus stress the brace has to be quite large and it only has an effect when it is worn. These aspects create challenges for long-term use of the brace in terms of compliance to the treatment. An HTO can achieve a true correction of the malalignment and is known to be able to postpone the need for knee arthroplasty for multiple years.[56-58] There is, however, a rehabilitation period of several months and, like every surgical procedure, risks are involved. Furthermore, a knee arthroplasty procedure after a previous HTO is more complex.[59] Although both treatments have been studied extensively and are used in daily clinical practice, to date, only one study compared the results of an HTO to an unloader brace.[60] This study was not a randomized trial, but a propensity matched study using 2 randomized controlled trial (RCT) datasets. Considering the possible confounding factors in a such a trial design, there is still a clear knowledge gap that warrants a randomized trial on the effects of both unloading treatments on clinical symptoms and progression of the disease.

Current osteoarthritis treatments focus on osteoarthritis that is visible on conventional radiography. Unfortunately, by the time these features appear, they are likely irreversible. On the other hand, in those experiencing initial osteoarthritis symptoms, there are often no or only subtle signs apparent on conventional radiography.[61] The true challenge lies in addressing osteoarthritis when it is still reversible. Early interventions, such as lifestyle adjustments or disease-modifying osteoarthritis drugs (DMOADs), could potentially alter the progression of the disease. Despite considerable effort in developing DMOADs, it unfortunately has been without resounding success so far.[1, 62] These drugs are being investigated in patients already displaying evident osteoarthritis features to comply with regulatory guidelines by the United States Food and Drug Administration and European Innovative Medicines Initiative.[63-66] Another reason for focusing on this patient group is that advanced osteoarthritis shows faster progression, theoretically allowing earlier observation of treatment effects. However, with this approach DMOAD therapy is probably initiated too late, as irreversible damage has already set in. Therefore, in the search and development of treatments for mild to moderate osteoarthritis, there is a need for imaging techniques that can display osteoarthritis at an earlier stage. Furthermore, they also should be able to detect subtle changes to serve as monitoring and evaluation tools for intervention studies' outcomes.

Imaging

Conventional radiography is still the gold standard for diagnosing osteoarthritis.[67, 68] Since radiography only shows the bones, osteoarthritis is primarily visible at an advanced stage when the cartilage has worn down to the point that the bones it covers have moved closer together. This so-called joint space narrowing is therefore an indirect representation of the

osteoarthritis.[69] Other signs of osteoarthritis on radiography include subchondral sclerosis, cysts and osteophytes. Because these signs arise over a long period of time, radiography is not sensitive enough to detect subtle changes. In order to diagnose osteoarthritis at an earlier stage and detect subtle changes, imaging techniques should probably focus on compositional assessment instead of morphological assessment. Furthermore, the degree of osteoarthritis should be expressed quantitatively in order to accurately monitor the effect of a treatment by making multiple images or scans over a period of time. Finally, an imaging technique preferably has a good (cross-sectional, longitudinal or predictive) correlation with clinical symptoms.[70-74] This way structural changes could be linked to the patient's complaints, which will help an accurate diagnosis. For conventional radiography, previous population studies have shown that there is no correlation between the complaints of osteoarthritis experienced by a person and the degree of osteoarthritis.[75-78]

Over the past 20 years, various imaging techniques have been developed with the aim of detecting osteoarthritis at an earlier stage and also be able to quantify the degree of the process. Especially in the field of magnetic resonance imaging (MRI), many techniques have been developed to assess the composition of the articular cartilage.[79, 80] Two well-established quantitative MR imaging techniques are transverse relaxation time (T2) mapping and delayed gadolinium enhanced MRI of cartilage (dGEMRIC).[79, 81-87] Other techniques include spin-lattice relaxation time constant in rotating frame (T1rho), glycosaminoglycan chemical exchange saturation transfer (gagCEST), dynamic contrast-enhanced (DCE) MRI and double-echo steady-state (DESS) sequences.[88, 89] Both T2 mapping and dGEMRIC assess the cartilage quality instead of the morphology, but do this in different ways. T2 mapping uses transverse (T2) relaxation times to quantify the hydration content, collagen fiber orientation and collagen network integrity of articular cartilage (Figure 4). As the collagen fiber orientation and collagen network integrity deteriorate with progression of the osteoarthritis, water is less bound within this network, resulting in higher T2 relaxation times in the affected cartilage areas.[88, 90] dGEMRIC uses a gadolinium-based MRI contrast agent that is administered intravenously or intra-articularly.[91] The contrast agent diffuses into cartilage areas where the glycosaminoglycan content is depleted. This glycosaminoglycan content increasingly decreases with the progression of the osteoarthritis. The contrast agent shortens the spin-lattice (T1) relaxation times of the lesions, which enables the technique to visualize the areas of degeneration and quantify the quality of the articular cartilage. Both the deterioration of collagen and the depletion of glycosaminoglycans happen before morphological changes of the cartilage occur. The techniques are therefore able to visualize osteoarthritis at an early stage and could be able to detect subtle changes.[91, 92]

In recent years, there has also been increasing attention for the use of nuclear techniques, such as single photon emission computed tomography - computed tomography (SPECT-CT), to quantify the osteoarthritis process.[93-95] SPECT-CT uses a radioactive tracer bound to a bisphosphonate. This bisphosphonate is absorbed into areas of active bone metabolism. As we know, subchondral bone metabolism is increased in osteoarthritic joints. The SPECT

scan is made a few hours after administration of the tracer, when the activity is registered using gamma cameras. By making a low-dose CT scan immediately after the SPECT scan, the images can be fused and the activity can be correlated to the anatomical region (Figure 4). Quantification of SPECT-CT has only been available for several years since the introduction of advanced iterative reconstruction techniques and software analysis tools.[96] Unlike various other imaging methods for osteoarthritis, SPECT-CT captures the current metabolic activity of the disease rather than focusing on its structural damage.

To date, quantitative imaging techniques for osteoarthritis have mainly been used for cross-sectional and longitudinal research studies in selected groups of patients. Two examples of large-scale longitudinal epidemiologic studies in which quantitative MR imaging techniques play a fundamental role are the Osteoarthritis Initiative and the Multicenter Osteoarthritis Study.[97-99] However, the utilization of quantitative imaging methods for evaluating the effects of interventions has been limited within clinical research and has not been implemented into clinical practice.[100-107] The integration of these imaging techniques as parameters for treatment outcomes presents several challenges. First, we need to know whether they are sensitive enough to detect subtle changes within a limited period of time. Moreover, the impact on quantitative imaging outcomes of patient and disease characteristics, the diversity among MRI scanner setups, and the presence of implanted materials in procedures like HTO, still lacks clarity and warrants further investigation. A more profound comprehension of these challenges can provide insights into how to effectively implement quantitative imaging in clinical research and clinical practice.

Aims and outlines of this thesis

Brace treatment and HTO are both well-established treatments for medial knee osteoarthritis.[108-110] However, the difference in effects on symptoms and structural progression between the non-surgical knee brace and the surgical osteotomy has not been compared in an RCT. Therefore, we designed a multicenter open-labelled RCT comparing both unloading therapies in patients with medial knee osteoarthritis and a varus knee malalignment. The primary objective of this study was to assess the difference in effect on knee pain between the valgus unloading knee brace compared to the HTO after one year of follow-up. In **Chapter 2,** we describe the clinical results of this RCT. The secondary aim was to investigate whether T2 mapping and quantitative SPECT-CT are able to detect changes in the composition of cartilage and subchondral bone activity, respectively, following the unloading treatments. These results are described in **Chapter 3**.

The additional research within this thesis delves into several considerations that need to be addressed in order to implement quantitative imaging, with T2 mapping in particular, as a diagnostic tool for early osteoarthritis detection or as an outcome tool to evaluate the effect of intervention studies.

First, knee osteoarthritis being a multifactorial disease means dealing with a wide range of patient and disease characteristics when performing research on this disease. We therefore evaluated knee cartilage T2 relaxation times and its association with factors like age, gender, BMI, prior traumatic injuries and clinical symptoms in an unselected clinical population with knee complaints in **Chapter 4**.

Second, studies into osteoarthritis treatment effects often necessitate large participant cohorts, frequently demanding multicenter studies. When applying quantitative imaging in these studies, an important concern is the variety of MRI scanner manufacturers and scanner models accessible in the market. In the context of MRI, factors such as field strength, coil type, and scan parameters notably influence quantitative imaging outcomes. Without knowledge of these influences, quantitative imaging techniques cannot be applied in multicenter studies. We therefore performed a study, described in **Chapter 5**, to explore the influence of different scanning equipment and scanning protocols on T2 mapping.

Third, when conducting quantitative MRI following an HTO, metal is present near the areas of cartilage being examined. The metal disrupts the MRI's magnetic field, causing artefacts in the images. This not only raises concerns about visible distortions, but also questions the reliability of using quantitative imaging near metal. To address this, **Chapter 6** presents an experimental study using human cadaver knees to investigate how metal implants affect T2 mapping.

Finally, as previously mentioned, various MRI techniques are available for evaluating cartilage quality. Combining various quantitative MRI methods provides a more comprehensive assessment of the osteoarthritis status because they assess distinct aspects of the articular cartilage, such as GAG or collagen content.[92, 111] In the case of combining dGEMRIC and T2 mapping, one technique requires a contrast agent, while the other does not. Current practice involves two separate scanning sessions, a time-consuming and less patient-friendly approach.[91, 112] An ideal scenario would involve integrating different techniques within a single session. To explore this, **Chapter 7** investigates whether T2 mapping and dGEMRIC can be combined into a single scanning session after administration of contrast agent.

Chapter 8 contains the general discussion on the study results of this thesis with recommendations for further research. **Chapter 9** provides a general summery of the studies included in this thesis and their results.

Figures

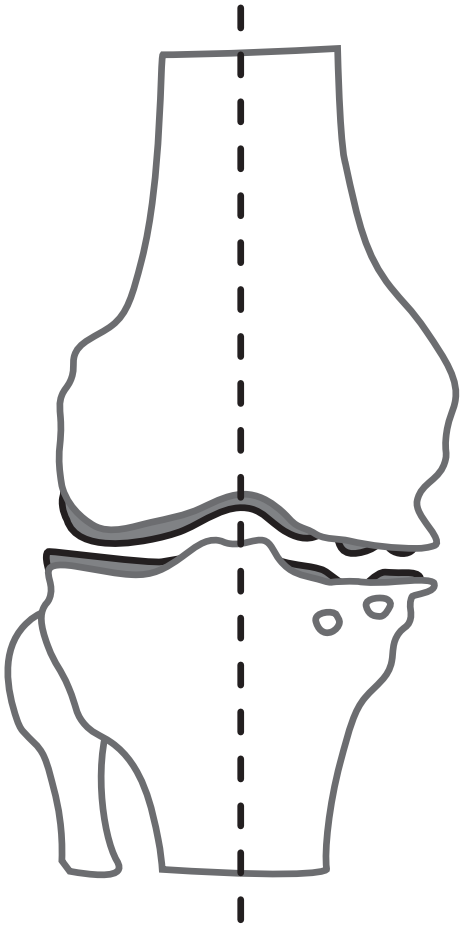


Figure 1. Illustration demonstrating characteristics of osteoarthritis. The image shows a healthy lateral knee compartment on the left and an affected medial joint compartment on the right with signs of cartilage deterioration, osteophytes and subchondral bone cysts.

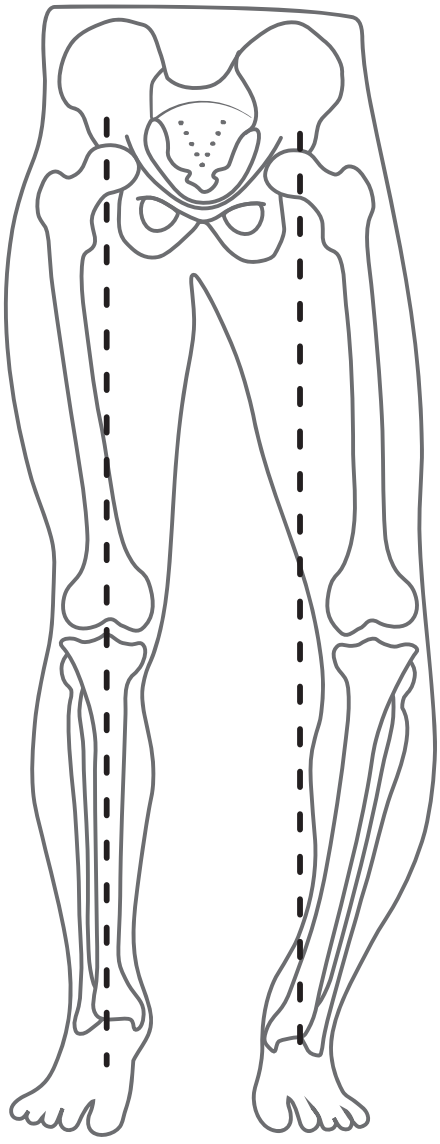


Figure 2. Illustration demonstrating a normal knee alignment of the right knee and a varus malalignment of the left knee.

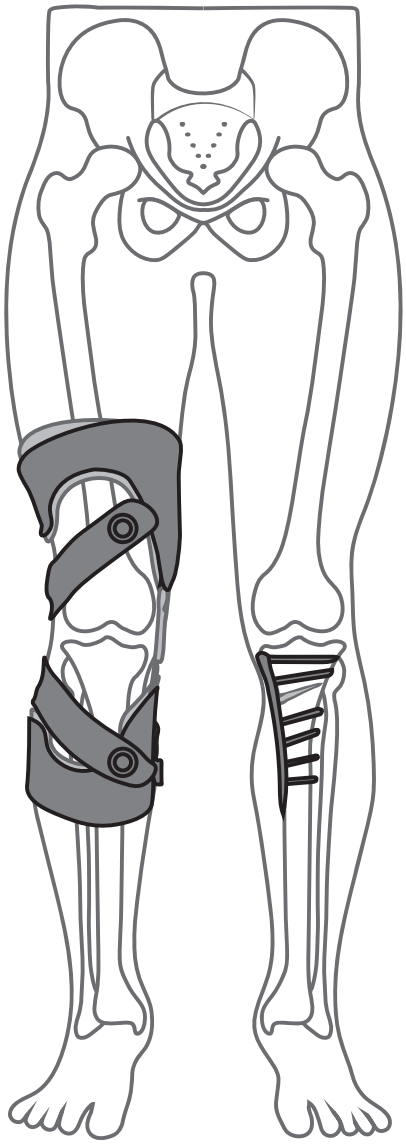


Figure 3. Illustration demonstrating a valgus unloading brace on the right knee and an opening wedge HTO on the left knee.

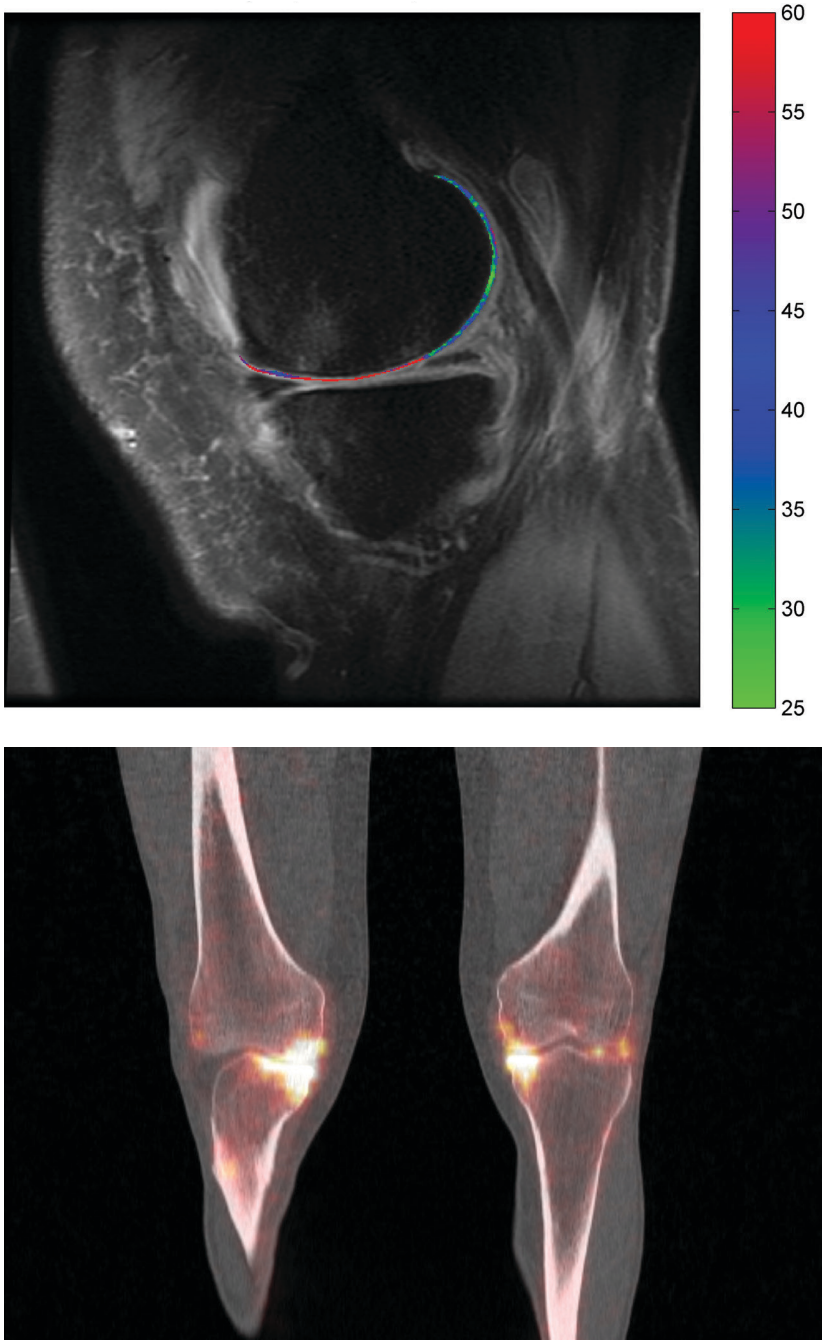
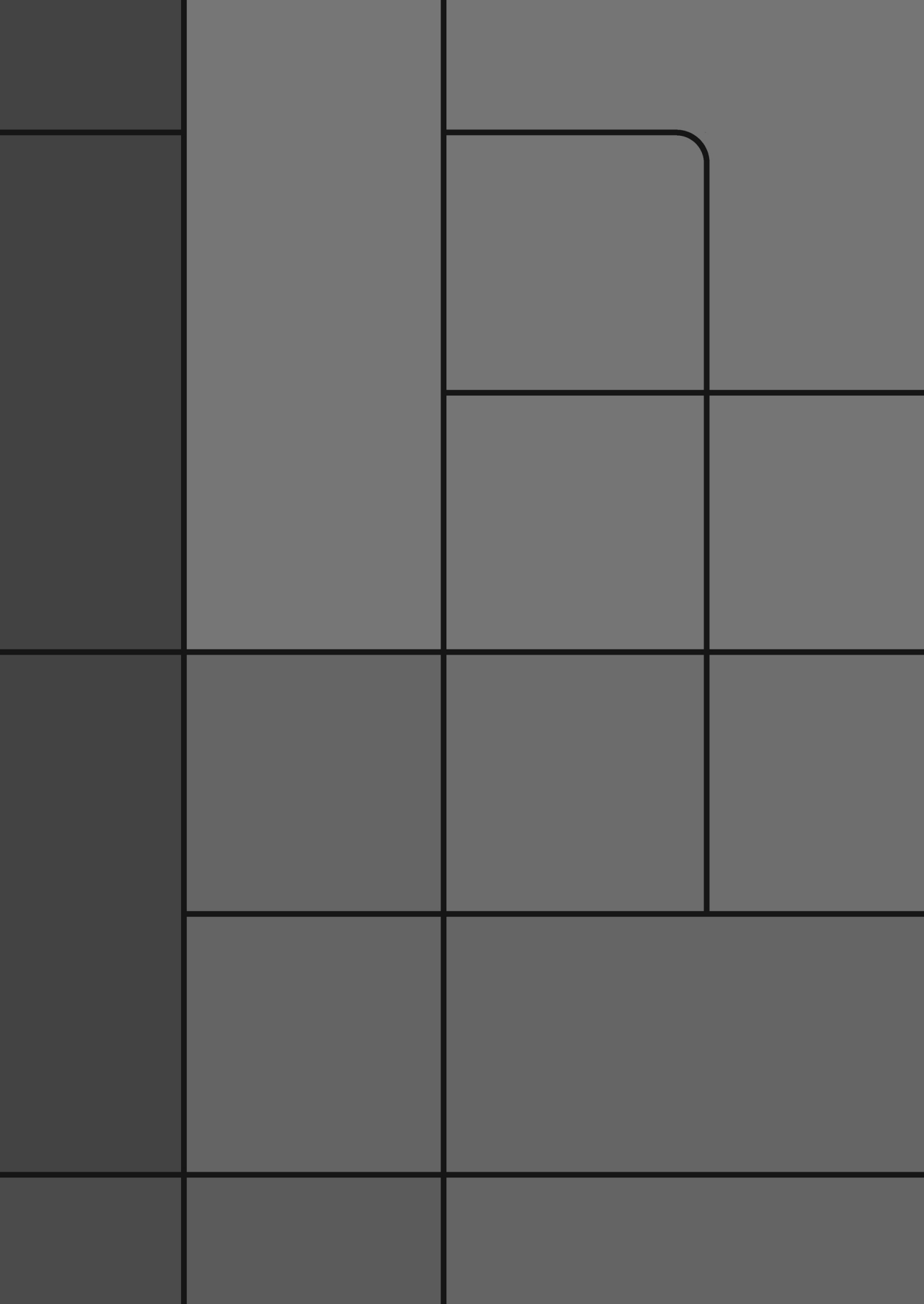


Figure 4. Top illustration demonstrating a T2 map of the femoral knee cartilage in a sagittal view. Higher T2 relaxation times (in milliseconds) represent a more deteriorated condition of the cartilage. Bottom image showing a fused coronal SPECT-CT image of a patient with bilateral medial knee osteoarthritis demonstrating high radioactive tracer uptake in the medial compartment of both knees.



Chapter 2

How should a young patient with medial knee osteoarthritis be treated? A randomized controlled trial comparing an unloader brace with a high tibial osteotomy

Mark Stam, Joost Verschueren, Mark V. van Outeren, Reinoud W. Brouwer, Robert D.A. Gaasbeek, Sorin G. Blendea, Eline M. van Es, Max Reijman, Sita M. A. Bierma-Zeinstra, BvO-study group (Rutger C.I. van Geenen, Ronald J. van Heerwaarden, Frank Th. G. Rahusen)

Submitted

Abstract

Background

For medial knee osteoarthritis (OA), operative and non-operative treatment options are available that aim to unload the affected medial knee compartment. Two widely applied unloading therapies are a valgus unloader brace and a high tibial osteotomy (HTO). To date, no study has compared the effects of an unloader brace with an HTO in a randomized setting.

Questions/Purposes

1. Is an HTO more effective in reducing knee pain compared to a valgus unloader knee brace in patients with symptomatic medial knee OA?
2. Is there a significant difference between both groups during follow-up in patient reported outcomes, painkiller use and adverse events?

Methods

We recruited patients from nine Dutch hospitals between August 2014 and February 2019 for an open-labeled multi-center randomized controlled trial. Patients aged 18 to 65 years with symptomatic medial compartmental knee OA were randomized to either a valgus unloader brace or an HTO. The primary outcome was the pain subscale of the Knee injury and Osteoarthritis Outcome score (KOOS) after one year. Secondary outcomes were: numeric rating scale (NRS) for pain, other subscales of the KOOS, the Intermittent and Constant Osteoarthritis Pain score (ICOAP) and the Hospital for Special Surgery scale (HSS). Patients were evaluated at 3, 6, 9, 12 and 24 months.

Results

A total of 51 patients were included in the study, of which 23 were randomized to the unloader brace and 28 to the HTO. The HTO, compared to the unloader brace, showed a significant and clinically relevant difference at 12 months of follow-up in KOOS pain of -27.7 (95% confidence interval: -43.0 to -12.5). Similar results were found for the secondary outcomes.

Conclusions

The difference in KOOS pain after 12 months between the unloader brace and HTO exceeded the minimal clinically important difference (MCID) for KOOS pain substantially. Therefore, this study suggests that on group level an HTO is more effective in reducing knee pain compared to an unloader brace.

Introduction

In up to 50% of knee osteoarthritis (OA) patients, the medial knee compartment is more affected than the lateral and patella-femoral compartment.[22, 23] Due to the negative impact of an active lifestyle on the survival of the prosthesis, a total knee arthroplasty (TKA) is not the first treatment choice for young patients with medial knee OA.[113-116] Notably, patients under 65 years old have a significantly higher TKA revision rate, ranging from 1.8% to 7%, compared to those over 65, where it is between 0.8% and 1%.[117] For medial knee OA, operative and non-operative treatment options are available that aim to unload the affected medial knee compartment.[116, 118-121] These interventions aim to alter the biomechanics of the knee and consequently reduce symptoms.[22, 24, 122-124] Ideally, they revoke or postpone the need for a TKA. Two widely applied unloading therapies are a valgus unloader brace and a high tibial osteotomy (HTO).

A valgus unloader brace is a popular non-operative treatment option for medial knee compartment OA.[125] The results of an unloader brace are promising concerning pain relief and improvement of function. However, compliance appears to be a challenge.[110, 118, 119, 123, 124, 126] An HTO intends to realign the limb and transfer the weight-bearing axis from the affected medial knee compartment to a slightly lateral position.[127-129] It has proven to be an effective treatment in reducing pain and functional symptoms.[130-132] Low conversion rates from HTO to TKA have been found, with reported 10-year survival rates ranging from 73% to 98%.[133-136] Nonetheless, HTO is a technically demanding procedure with its inherent complications.[113, 120, 130, 137, 138]

To date, no study has compared the effects of an unloader brace with an HTO in a randomized setting. The aim of this multi-center randomized controlled trial was to compare the effects on knee pain of a valgus unloader knee brace with a high tibial osteotomy in patients with symptomatic medial knee OA. We hypothesize that an HTO would result in more alleviation of knee pain compared to an unloader brace since an HTO provides a more permanent structural correction of malalignment.

Patients/Methods

Study design and setting

We conducted an open-labeled multi-center randomized controlled trial in patients with medial compartmental knee OA. The trial was carried out in nine hospitals in the Netherlands, and patients were recruited between August 2014 and February 2019. The Erasmus MC University Medical Center ethics committee approved the research protocol, and all patients gave written informed consent. The trial was registered in the Dutch Trial Register prior to the inclusion of the first subject (NTR number NL4200). Reporting follows the Consolidated Standards of Reporting Trials (CONSORT) guidelines.[139]

Participants

Patients between 18 and 65 years consulting an orthopaedic surgeon in one of the participating centers for symptomatic medial knee OA were eligible to participate. The criteria for inclusion were: knee pain located over the medial tibiofemoral compartment of the knee, knee pain for more than 3 months, with a severity of minimally 3 on a Numeric Rating Scale (NRS) (range 0 to 10), radiographic signs of medial knee OA with a Kellgren & Lawrence score of grade 1 to 3, and presence of varus malalignment with a maximum of 14 degrees as measured on a whole leg radiograph. Patients were excluded when one of the following criteria was present: radiographic OA of the lateral compartment with a Kellgren & Lawrence score of grade 2 or higher, rheumatoid arthritis, grade-3 collateral ligament laxity, range of motion of < 100°, a flexion contracture of > 10°, history of fracture or previous open operation of the lower limb or lateral meniscectomy, past use of an orthopaedic knee brace for knee OA in the same knee, contralateral HTO or brace if that knee has been included in this trial (thus, if both knees were symptomatic, the most affected knee was included), uncertainty about ability to attend the follow-up measurements and insufficient understanding of the Dutch language, spoken and/or written. To determine the patient's eligibility, standing AP and lateral knee and long-leg radiographs were taken and assessed by the attending orthopaedic surgeon of the participating hospital where the patient presented. The radiographs were used to measure the presence and severity of knee OA with the Kellgren & Lawrence score and the varus malalignment with the hip-knee-ankle (HKA) angle. The HKA-angle was defined as the angle between two prolonged lines: one line from the center of the femoral head to the top of the femoral notch and a second line from the center of the ankle to the center of the tibial spines.[140] Patients were registered for the study by their own orthopaedic surgeon and referred to the coordinating hospital (Erasmus MC University Medical Center) for enrollment and measurements. One specific researcher conducted all measurements. The actual treatment was provided at the patient's own hospital.

Randomization, blinding and treatment allocation

Following informed consent and baseline measurements, patients were randomized to one of the two treatment groups in a 1:1 ratio. Randomization was stratified for experience of the orthopaedic surgeon with performing an HTO procedure (more or less than 20 HTO's per year) and sex. The coordinating researcher contacted one researcher (not otherwise associated with the trial) who allocated treatment arms using computer-generated random numbers (central randomization). The type of randomization was stratified balanced block randomization. Treatment arms were allocated in block sizes varying from 2 to 6. Because of practical reasons, the orthopaedic surgeon and the patient were not blinded for the intervention.

Interventions

Valgus unloader brace

Before the initiation of the RCT, an internal pilot study was performed to select the most appropriate brace for the trial. Three widely available valgus unloader braces in the Netherlands were compared regarding comfort, convenience and pain relief in patients with medial knee OA from the orthopaedic clinic of one of the participating centers. Nine patients, not participating in the RCT, wore each brace for 2 weeks. Based on their experiences, the Össur Unloader One brace (Össur hf., Reykjavík, Iceland) was chosen for its effect on pain reduction and its patient-friendly features. The brace was fitted and customized to the patient's knee by an orthotist at the start of the treatment. The brace had to be worn with daily activities throughout the day during the 2-year follow-up period. Medication use was standardized for both groups and was given according to existing Dutch guidelines, according to the WHO analgesic ladder.[141, 142]

High tibial osteotomy

Patients received a medial open or lateral closed wedge high tibial osteotomy, according to the preferred surgical technique in the participating hospitals. The open wedge osteotomy was created through a medial approach to the proximal tibia by making a saw cut a few centimeters below the joint surface while preserving the lateral cortex. Subsequently, the saw cut was opened from the medial side, causing a valgus alignment of the lower leg as the lateral cortex acted like a hinge. The created open wedge was fixed on the medial side of the tibia with a titanium plate and screws (TomoFix, DePuy Synthes, PA, USA). In the case of the closed wedge osteotomy, the proximal tibia was approached through an anterolateral approach. The proximal tibia was cut a few centimeters below the joint surface while preserving the medial cortex. A second saw cut was made to create a bony wedge that was removed. The resulting wedge-shaped space was then closed, leading to valgus alignment of the lower leg as the medial cortex acted as a hinge. The anterior portion of the proximal part of the fibular head, which represents the anterior part of the proximal tibiofibular syndesmosis, was resected. No fibula osteotomy was performed. Subsequently, fixation was achieved using a titanium plate and srews (TomoFix, DePuy Synthes, PA, USA) or chrome-cobalt staples (Stepped High Tibial Osteotomy Staples, Stryker, MI, USA). The thickness of the wedge was calculated in advance to achieve the desired degree of correction. In both osteotomy techniques, fluoroscopy was used during the procedure to determine the position of the osteotomy planes and to monitor the degree of correction. The aim of both techniques was to create a valgus knee alignment of 4 degrees. The day after the operation, patients were mobilized with partial weight bearing of the operated leg. Patients were discharged when they were able to walk without assistance, using two crutches, and with acceptable wound healing. After the initial post-operative mobilization, physiotherapy was recommended during the post-operative rehabilitation.

Measurements

The primary outcome was knee pain after one year of follow-up assessed with the pain subscale of the Knee injury and Osteoarthritis Outcome score (KOOS). The KOOS questionnaire consists of five subscales: pain, symptoms, activities of daily living (ADL), sports and quality of life (QoL).[143] A score is calculated for each subscale, which ranges from 0 to 100, with 100 being the optimal score. Secondary outcomes were: knee pain assessed with the KOOS pain subscale after 24 months, the numeric rating scale (NRS) for pain severity, other subscales of the KOOS, the Intermittent and Constant Osteoarthritis Pain score (ICOAP) and the Hospital for Special Surgery scale (HSS).[144-146] In addition, painkillers, self-reported complaints and (serious) adverse events were evaluated during follow-up by questionnaires and medical records. NRS-pain ranged from 0 to 10, where 0 represented no pain.[144] The ICOAP is a questionnaire comprised of 11 items about intermittent and constant knee pain, which is converted into a pain score which ranges from 0 to 44, with 0 representing no pain.[146] HSS, which was conducted by the researcher, is a scale with subscores about pain, range of motion, instability, flexion deformity, alignment, leg extension and medical aids, which add up to a total score with a maximum of 100 points representing no knee complaints.[145] Adverse events were self-reported by the patient with questionnaires during follow-up. Serious adverse events were registered by the participating centers. All reported complications and re-interventions that could have been objectified and reasonably have been a consequence of the given treatment were analyzed as (serious) adverse events. Patients completed all questionnaires digitally at baseline and 3, 6, 9, 12 and 24 months after randomization, except for the KOOS questionnaire. The KOOS questionnaire was filled in at baseline, 12 and 24 months. Study data were collected and managed using GemsTracker electronic data capture tool hosted at the Erasmus MC.[147] All included patients visited the coordinating hospital at baseline and after one year of follow-up for a physical examination for the HSS rating scale and additional quantitative Magnetic Resonance Imaging (MRI) and single photon emission computed tomography - computed tomography (SPECT-CT).

Sample size

When we calculated the sample size, no studies on minimal clinically important difference (MCID) for the KOOS score were available. We based our initial sample size calculation on detecting a difference with an effect size of 0.5 in favor of a surgical intervention compared to a non-operative strategy, with 80% power and a two-side type 1 error of 5%. To accommodate a potential loss to follow-up of 15% over 1 year, the target sample size was set to 124 patients (62 per group). However, the study experienced a delay because of problems in recruiting patients willing to be randomized to surgical treatment or non-surgical treatment. Based on expected outcomes in newly published literature, and baseline standard deviations of the KOOS subscale pain in our study population, we adjusted our sample size in agreement with the grant supplier and the Dutch Orthopaedic Association. We determined that 28 participants per group (a total of 56) would be sufficient, with the aim to enroll 64 patients, allowing for a potential dropout rate of up to 15% over a one-year period.[119] Finally, the recruitment of patients was finished in 2019 in agreement with the grant supplier.

Statistical analysis

Patients were analyzed according to their randomization group. To answer our primary research question, we used a linear regression model with KOOS pain subscale after 1 year as dependent variable, adjusted for age, sex, surgeon's experience and KOOS pain at baseline. We checked the following model assumptions: linearity, multicollinearity, homoscedasticity and normality and independence of residuals in the linear regression model. None of the assumptions were violated. A linear mixed model analysis was used to assess the secondary outcomes. We used an unstructured covariance structure and a Restricted Maximum Likelihood (REML) model for estimation. The fixed factors added to the model were the interaction term of time by treatment (the multiplication follow-up and randomization), age, sex and experience of the surgeon. The model assumptions of linearity, homoscedasticity and normality of residuals were assessed and considered not violated. 95% confidence intervals were reported. IBM SPSS statistics was utilized for all analyses.

Results

Patients

Of the 107 patients enlisted for the study, 21 strongly preferred brace treatment and also 21 patients strongly preferred the osteotomy. These patients were unwilling to be randomized and were therefore excluded. Seven patients did not meet our inclusion criteria and another 7 patients refrained from treatment. This resulted in a final study population of 51 patients. Twenty-three patients were randomized to the brace and 28 to the HTO. The response rate of one year follow-up of KOOS-pain score was 91% for the brace and 96% for the HTO group. After randomization, 3 patients (3/23, 13%) from the brace group crossed over to the HTO group, 1 patient (1/23, 4%) before the 12 months' time point and 2 patients (2/23, 9%) between 12 and 24 months' time point. Three patients (3/28, 11%) in the HTO group did not receive an HTO due to patient's preference or clinician's choice to refrain from surgery due to minimal knee symptoms or patellofemoral knee osteoarthritis on MRI and SPECT-CT. Three patients (3/23, 13%) in the brace group converted to an unicompartmental knee arthroplasty (UKA) or a total knee arthroplasty (TKA) and one patient (1/28, 4%) in the HTO group converted to a TKA during the 24 months follow-up. Detailed information can be found in Figure 1. Table 1 provides information on the baseline characteristics of the included patients. Age and KOOS pain score at baseline differed between the brace and HTO group. Patients in the brace group were on average 5.2 years younger (49.9 vs 55.1 years of age) and scored 7.3 points higher on the KOOS pain scale at baseline (43.1 vs 35.8).

Primary outcome

The adjusted estimated mean KOOS pain score at 12 months follow-up for patients allocated to the brace was 48.9 (95% Confidence Interval (CI): 44.3 to 53.5) and 70.5 (95% CI: 66.5 to 74.4) for patients allocated to the HTO (Table 2). The improvement in KOOS pain scores at

12 months follow-up was 5.8 (95% CI: 2.0 to 9.5) for the brace group and 34.6 (95% CI: 31.0 to 38.1) for the HTO group.

Secondary outcomes

The adjusted estimated mean KOOS pain score at 24 months follow-up for patients allocated to the brace was 49.7 (95% CI: 47.5 to 51.9) and 76.0 (95% CI: 73.6 to 78.4) for patients allocated to the HTO (Table 2).The adjusted estimated means of the other secondary outcomes are presented in Table 3. All secondary outcomes showed a statically significant difference in improvement between both groups in favor of the patients allocated to the HTO group. The HTO group demonstrated superior results for the secondary outcomes compared to the brace group at all follow-up points.

Adverse events

Self-reported complaints are presented in Table 4. Seventeen of the 23 patients treated with a brace (17/23, 74%) reported a total of 23 complaints. The most frequent complaints of the brace were skin irritation (16/23, 70%) and numbness (5/23, 22%). In comparison, 19 of the 25 treated patients in the HTO group (19/25, 76%) reported a total of 29 complaints. Irritation (12/25, 48%) and numbness (11/25, 44%) were the most common complaints. Other self-reported complaints were wound infection (3/25, 12%) and post-surgery bleeding (1/25, 4%). Ten of the 25 treated patients in the HTO group underwent plate removal during the course of the study (10/25, 40%). The average duration from HTO to plate removal was 8.8 months (SD 2.5). Six plates were removed before the 12 months' time point and four plates were removed between 12 and 24 months. Finally, a higher conversion to a TKA was seen in the brace group (3/23, 13%) than in the HTO group (1/25, 4%) during the course of the study. In the brace group, 3 patients converted to a TKA before the 12 months' time point and 1 patient between 12 and 24 months. In the HTO group, 1 patient converted to a TKA between 12 and 24 months. The average duration from the start of the brace treatment to conversion to a TKA was 7.7 months (SD 1.2) and the duration from HTO to conversion to a TKA was 12 months. In the HTO group, one patient received an HTO for the contralateral knee during follow-up.

Painkiller use

Painkiller use is listed in Table 5. At baseline, 43% (10/23) of the patients allocated to the brace used painkillers, while 75% (21/28) of the patients allocated to the HTO used painkillers. After 12 months, 50% (10/20) of the patients allocated to the brace and 30% (8/27) of the patients allocated to the HTO used painkillers. After 24 months, these proportions were 47% (8/17) and 24% (6/26).

Discussion

The primary aim of this randomized controlled trial was to compare the effects on knee pain of an unloader brace with an HTO in patients with medial knee OA. The results of this study show that on group level an HTO is more effective in reducing knee pain compared to an unloader brace. The difference in improvement between the brace and HTO group for KOOS pain during the first 12 months was almost double the minimal clinically important difference (MCID) for KOOS pain of 15.4.[148] We found an improvement in the brace group for KOOS pain of 5.8 after one year. This improvement was reasonable similar to earlier studies, which found changes on this KOOS subscale after one year ranging from 6.8 to 8.8.[126, 149, 150] In the HTO group, we found an increase from baseline to one year of follow-up for KOOS pain of 34.6. This is in accordance with studies performed by De Pieri et al. and Jacquet et al.[151, 152] De Pieri et al. reported a median change in KOOS pain of 31.9 and Jacquet et al. found an improvement after one year of 35. Till date, the study of Van Outeren et al. is the only study which performed a comparison between a brace and an HTO in patients with medial knee OA.[60] Although Van Outeren et al. showed that the HTO is more effective in reducing knee pain than a brace, the difference was so small that the authors questioned the benefits of a surgical treatment over the brace treatment. Patients undergoing HTO usually have a postoperative treatment and recovery period lasting up to 6 months in most of the patients.[153, 154] Our findings indicate that patients who underwent HTO show significant symptom improvement already at time points before the one-year follow-up. This study demonstrates that HTO could rapidly improve pain and function for younger patients with medial knee OA. Noteworthy were the three cross-overs and the three conversions to TKA in the 23 patients allocated to brace treatment. This high percentage of patients in the brace group switching to a different treatment might be attributable to ineffectiveness of the brace.[118] In both groups, negative effects of the treatment were experienced. The majority of patients allocated to the brace complained about skin irritation and/or numbness when wearing the brace. This is supported by previous research that recorded skin irritation, bad fit and discomfort caused by the brace.[118, 119, 149] The discomforts while wearing the brace, in combination with minimal treatment effect of the brace, impedes therapy compliance, according to the literature.[118, 126] Similar to other surgical procedures, HTO carries risks. Irritation due to hardware material was frequently reported in our study, which necessitated plate removal in 44% of the HTO patients during the course of the study. In addition, wound infections were recorded, with one patient requiring reoperation. Documented complications in earlier studies included hardware failure, intraoperative fracture of the lateral bone, infection, loss of correction, nerve injury and nonunion.[155-157] This emphasizes the importance of considering adverse events during treatment decision-making. The findings of this study have to be interpreted in light of its strengths and limitations. Strengths of this study were the randomization which contributes to the internal validity of the study and the multicenter design which warrants generalizability of our findings. Our internal pilot study, in which we selected the most appropriate brace regarding comfort, convenience and pain relief, ensured the best possible brace comparator for the HTO. The principal limitation of our RCT was the relatively small sample size of 51

patients. The initially calculated sample size was not reached due to experienced difficulties during the enrollment phase as a result of multiple reasons. Firstly, numerous patients expressed a strong preference for either of the treatments and consequently refused to participate in randomization. Secondly, the considerable travel distance from a recruiting center to the coordinating hospital deterred some patients from participating. Thirdly, the takeover and subsequent policy change of one of the potentially largest recruiting centers resulted in a diminished pool of potential candidates for the study. Fourthly, privacy regulations (General Data Protection Regulation (GDPR)) limited the possibility of active search for eligible patients within medical records, necessitating researchers to rely on the treating orthopaedic surgeons for recruitment. Despite the relatively small sample size, we identified an unequivocally clinically relevant difference between the treatment arms. Another limitation was a potential random sampling error due to baseline differences in age and KOOS pain. However, our primary outcome was adjusted for these baseline imbalances. A high frequency of cross-overs and conversions to TKA in the brace group was seen, which might have resulted in an overestimation of the treatment effect of the brace. This was supported by our sensitivity analysis (Supplementary Table) which demonstrates the as-treated results. This analysis showed an even larger between-group difference for our primary outcome. For that reason, the as-randomized results should be interpreted with caution. An additional limitation was that the type of intervention did not allow blinding of patients for the intervention. Therefore, the performance of surgery could potentially have resulted in a larger placebo effect in patients allocated to HTO.[158] In addition, the HTO group lacked a standardized procedure due to the performance of two types of osteotomies (open and closed wedge HTO) and the variation in surgical techniques and surgeons among the participating centers. However, we expect that the potential impact of this variation is limited due to two reasons. Firstly, there were no clinically relevant differences in clinical outcomes reported between open and closed HTO.[159] Secondly, the randomization was stratified for experience of the surgeon. Furthermore, the reported varus angles were subject to interobserver bias, as they were measured by the different treating orthopaedic surgeons. Nevertheless, the randomization process would likely have eliminated this accidental bias. A final limitation was that the patients were not instructed to refrain from painkillers for a certain restricted time before filling in the pain questionnaires. The brace group, however, showed more pain killer use than the HTO group at 12 and 24 months, indicating that difference in pain medication use cannot have caused the differences in outcome. The findings of our study suggest that on group level an HTO is more effective in alleviating knee pain after one year compared to a brace. The high number of conversions to TKA/UKA and cross-overs to HTO questions the effectiveness of the brace as well. Based on these results, HTO appears more successful in achieving the treatment objectives than the brace. Hence, surgeons should consider an HTO in younger patients with medial knee OA, while acknowledging the potential complications.

Tables

Table 1. Baseline characteristics of study population

	Brace (n=23)	HTO (n=28)
Age, years	49.9 (6.8)	55.1 (6.5)
Male sex, n (%)	14 (61)	17 (61)
BMI, kg/m²	29.0 (4.1)	29.8 (4.4)
Left leg affected, n (%)	10 (44)	15 (54)
Varus angle, degrees	6.7 (3.1)	5.7 (2.3)
Paid work, n (%)	15 (65)	21 (75)
Duration of symptoms, n (%)		
1-3 months	1 (4)	0 (0)
3-6 months	2 (9)	3 (11)
6-12 months	7 (30)	11 (39)
>12 months	13 (57)	14 (50)
KOOS pain	43.1 (3.0)	35.8 (2.7)

Data are shown as mean (SD)
KOOS = Knee Osteoarthritis Outcome Score

Table 2. Primary outcome

	Brace (n=23)	HTO (n=28)	Between group difference
KOOS pain after 12 months	48.9 (44.3 to 53.5)	70.5 (66.5 to 74.4)	-27.7 (-43.0 to -12.5)
Improvement KOOS pain during first 12 months	5.8 (2.0 to 9.5)	34.6 (31.0 to 38.1)	-29.3 (-44.1 to -14.6)

Data are presented as unstandardized predicted means and regression coefficients with 95% confidence interval in brackets
KOOS = Knee Osteoarthritis Outcome Score
KOOS pain after 12 months was known for 48 of the 51 patients
KOOS pain was adjusted for age, sex, surgeon's experience and KOOS pain at baseline

Table 3. Secondary outcomes

	T=0	T=3	T=6	T=9	T=12	T=24
KOOS						
Pain						
Brace (n=23)	42.7 (36.7 to 48.7)	na	na	na	48.8 (37.6 to 60.0)	51.3 (39.6 to 63.1)
HTO (n=28)	34.5 (29.2 to 39.8)	na	na	na	69.6 (59.6 to 79.5)	71.6 (61.1 to 82.1)
Between group difference	8.2 (0.0 to 16.4)	na	na	na	-20.7 (- 35.8 to -5.7)	-20.3 (-36.1 to -4.4)
Symptoms						
Brace (n=23)	50.4 (43.0 to 57.8)	na	na	na	56.5 (46.1 to 66.8)	56.0 (46.2 to 65.9)
HTO (n=28)	44.4 (37.9 to 51.0)	na	na	na	67.0 (57.8 to 76.2)	68.7 (60.0 to 77.4)
Between group difference	6.0 (-4.2 to 16.1)	na	na	na	-10.5 (-24.5 to 3.5)	-12.7 (-26.0 to 0.7)
ADL						
Brace (n=23)	46.4 (39.4 to 53.4)	na	na	na	56.1 (44.1 to 68.1)	57.5 (46.5 to 68.6)
HTO (n=28)	44.3 (38.1 to 50.6)	na	na	na	68.5 (57.8 to 79.1)	73.3 (63.5 to 83.1)
Between group difference	2.0 (-7.6 to 11.7)	na	na	na	-12.3 (-28.5 to 3.8)	-15.8 (-30.7 to -0.9)
Sports and recreation						

Table 3. Continued

	T=0	T=3	T=6	T=9	T=12	T=24
Brace (n=23)	17.9 (8.7 to 27.1)	na	na	na	19.5 (6.2 to 32.9)	31.4 (16.4 to 46.3)
HTO (n=28)	13.5 (5.4 to 21.7)	na	na	na	39.4 (27.6 to 51.2)	42.9 (29.6 to 56.2)
Between group difference	4.4 (-8.2 to 17.0)	na	na	na	-19.8 (-37.8 to -1.8)	-11.5 (-31.7 to 8.6)
QoL						
Brace (n=23)	26.3 (19.8 to 32.7)	na	na	na	31.4 (20.5 to 42.4)	38.2 (26.2 to 50.3)
HTO (n=28)	23.7 (17.9 to 29.4)	na	na	na	49.9 (40.2 to 59.7)	55.8 (45.0 to 66.6)
Between group difference	2.6 (-6.3 to 11.5)	na	na	na	-18.5 (-33.3 to -3.7)	-17.6 (-33.9 to -1.3)
NRS-pain						
At rest						
Brace (n=23)	5.4 (4.5 to 6.4)	4.7 (3.5 to 5.8)	5.5 (4.4 to 6.6)	5.1 (4.0 to 6.3)	4.4 (3.4 to 5.4)	4.6 (3.3 to 5.8)
HTO (n=28)	5.3 (4.5 to 6.2)	3.9 (2.8 to 5.0)	2.8 (1.8 to 3.8)	2.6 (1.5 to 3.6)	2.3 (1.4 to 3.1)	2.4 (1.3 to 3.4)
Between group difference	0.1 (-1.2 to 1.4)	0.7 (-0.8 to 2.4)	2.7 (-4.2 to -1.2)	2.6 (1.0 to 4.1)	2.1 (0.8 to 3.5)	2.2 (0.6 to 3.8)
During activity						
Brace (n=23)	7.7 (6.9 to 8.4)	5.6 (4.4 to 6.7)	6.2 (5.0 to 7.4)	6.1 (4.9 to 7.3)	6.5 (5.3 to 7.7)	6.2 (4.9 to 7.6)

Table 3. Continued

	T=0	T=3	T=6	T=9	T=12	T=24
HTO (n=28)	7.9 (7.3 to 8.6)	6.0 (5.0 to 7.0)	4.8 (3.8 to 5.9)	4.3 (3.2 to 5.3)	3.7 (2.7 to 4.8)	3.3 (1.7 to 4.8)
Between group difference	-0.2 (-1.3 to 0.8)	-0.4 (-1.9 to 1.1)	1.4 (-0.2 to 3.0)	1.9 (0.2 to 3.4)	2.8 (1.2 to 4.4)	3.0 (1.1 to 4.8)
HSS						
Brace (n=23)	72.3 (68.2 to 76.4)	na	na	na	77.5 (72.0 to 83.1)	na
HTO (n=28)	71.6 (68.0 to 75.3)	na	na	na	86.0 (81.0 to 91.1)	na
Between group difference	0.7 (-4.9 to 6.4)	na	na	na	-8.5 (-16.1 to -0.9)	na
ICOAP						
Intermittent						
Brace (n=23)	13.3 (11.2 to 15.3)	12.6 (10.3 to 15.0)	10.9 (8.2 to 13.6)	11.5 (8.7 to 14.3)	11.0 (8.4 to 13.7)	10.8 (7.8 to 13.7)
HTO (n=28)	14.0 (12.2 to 15.8)	10.6 (8.5 to 12.7)*	8.9 (6.5 to 11.3)*	8.4 (6.0 to 10.9)*	7.1 (4.8 to 9.5)	5.9 (3.3 to 8.4)
Between group difference	-0.8 (-3.5 to 2.0)	2.1 (-1.1 to 5.3)	2.0 (-1.6 to 5.7)	3.1 (-0.7 to 6.9)	3.9 (0.3 to 7.5)	4.9 (1.0 to 8.8)
Constant						
Brace (n=23)	9.8 (7.9 to 11.8)	8.8 (6.6 to 11.0)	8.2 (5.7 to 10.7)	8.6 (6.0 to 11.2)	8.3 (6.0 to 10.7)	7.7 (5.2 to 10.2)
HTO (n=28)	11.3 (9.6 to 13.1)	8.2 (6.2 to 10.1)*	5.9 (3.7 to 8.0)**	6.5 (4.2 to 8.8)**	5.1 (3.0 to 7.1)	4.6 (2.4 to 6.7)

Table 3. Continued

	T=0	T=3	T=6	T=9	T=12	T=24
Between group difference	- 1.5 (-4.0 to 1.0)	0.7 (-2.4 to 3.7)	2.3 (-1.0 to 5.7)	2.1 (-1.4 to 5.6)	3.3 (0.1 to 6.4)	3.2 (-0.2 to 6.5)
Total						
Brace (n=23)	23.2 (19.6 to 26.9)	21.6 (17.1 to 26.1)	19.2 (14.2 to 24.3)	20.3 (15.0 to 25.6)	19.5 (14.6 to 24.4)	18.5 (13.2 to 23.9)
HTO (n=28)	25.3 (22.1 to 28.6)	18.7 (14.7 to 22.7)	14.7 (10.2 to 19.2)	15.0 (10.3 to 19.6)	12.2 (7.8 to 16.5)**	10.4 (5.8 to 15.1)
Between group difference	-2.1 (-7.1 to 2.9)	2.9 (-3.2 to 9.0)	4.5 (-2.3 to 11.4)	5.3 (-1.7 to 12.4)	7.3 (0.7 to 14.0)	8.1 (0.9 to 15.3)

Data are presented as adjusted mean estimate with 95% confidence interval in brackets
Na = Not applicable
KOOS = Knee Osteoarthritis Outcome Score
NRS = Numeric rating scale
HSS = Hospital for Special Surgery Knee-Rating Scale
ICOAP = The intermittent and constant pain score
A linear mixed model was utilized for the analysis.
Outcomes were adjusted for age, sex and surgeon's experience

Table 4. Adverse events

Randomized as:	**Brace (n=23)***		**HTO (n=28)****
Treated as:	**Brace (n=23)**	**HTO (n=4)**	**HTO (n=25)**
Brace adverse events			
Patients with complaints, n (%)	16 (70)		
Overall complaints, n	21		
Patient reported complaints, n (%)			
Skin irritation	16 (70)		
Numbness	5 (22)		
Serious adverse events, n (%)			
Conversion to TKA	3 (13)		
HTO adverse events			
Patients with complaints, n (%)		2 (50)	19 (76)
Overall complaints, n		2	27
Patient reported complaints, n (%)			
Irritation		1 (25)	12 (48)
Numbness		1 (25)	11 (44)
Wound infection		0 (0)	3 (12)
Post-surgery bleeding		0 (0)	1 (4)
Serious adverse events, n (%)			
Plate removal		0 (0)	10 (40)
Conversion to TKA		0 (0)	1 (4)
Reoperation for wound infection		0 (0)	1 (4)

*Three patients crossed-over to HTO
**Three patients did not undergo an HTO
TKA = Total knee arthroplasty

Table 5. Pain medication use

		T0	T3	T6	T9	T12	T24
		n=23	**n=21**	**n=18**	**n=16**	**n=20**	**n=17**
Brace (n=23)	No painkillers	13 (57)	15 (71)	13 (72)	8 (50)	10 (50)	9 (53)
	Paracetamol	4 (17)	3 (14)	1 (6)	1 (6)	4 (20)	6 (35)
	NSAID	4 (17)	1 (5)	2 (11)	5 (31)	4 (20)	2 (12)
	Opioid	2 (9)	2 (10)	2 (11)	2 (13)	2 (10)	0 (0)
		n=28	**n=25**	**n=24**	**n=22**	**n=27**	**n=26**
HTO (n=28)	No painkillers	7 (25)	3 (12)	9 (38)	12 (55)	19 (70)	20 (76)
	Paracetamol	9 (32)	5 (20)	8 (33)	5 (23)	4 (15)	2 (8)
	NSAID	11 (39)	10 (40)	4 (17%)	3 (13)	3 (11)	2 (8)
	Opioid	1 (4)	7 (28)	3 (12)	2 (9)	1 (4)	2 (8)

Data are presented as n (%)
The painkiller with the highest analgesic potency used by the patient is shown in the table
NSAID = Non-Steroidal Anti-Inflammatory Drugs
Paracetamol = Acetaminophen

Figures

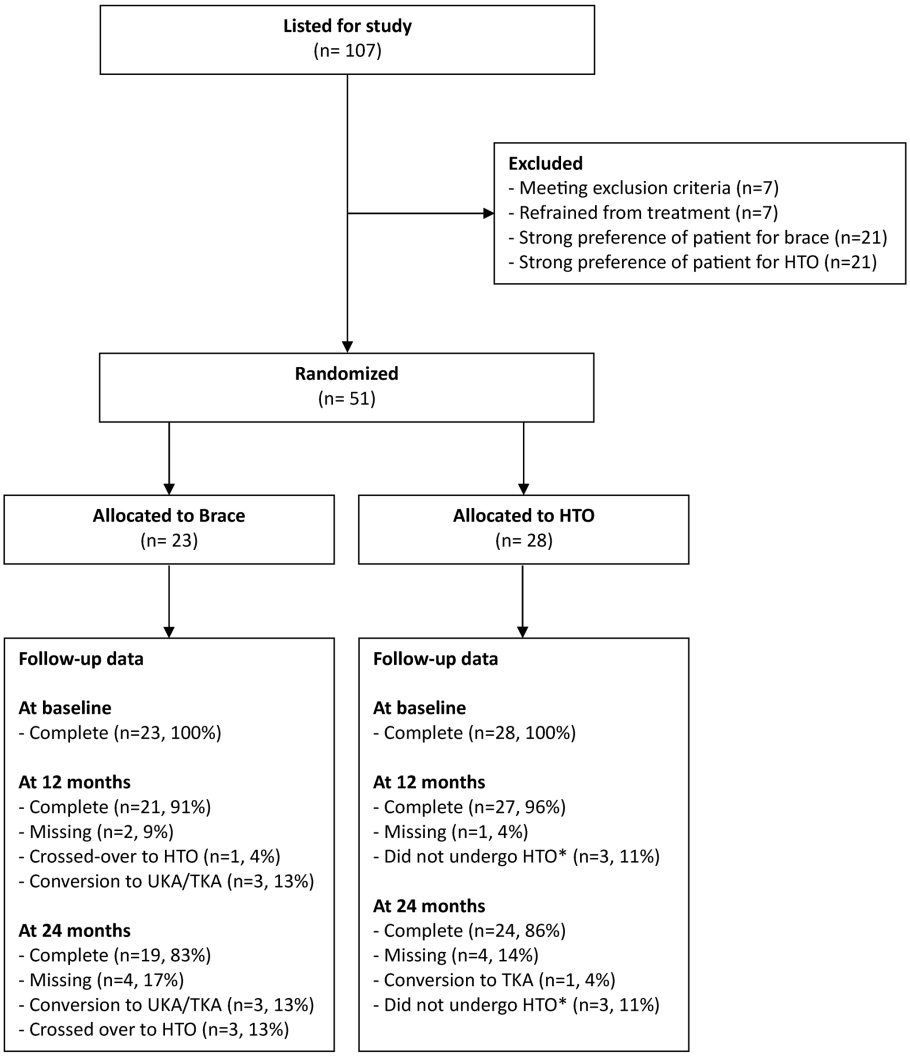
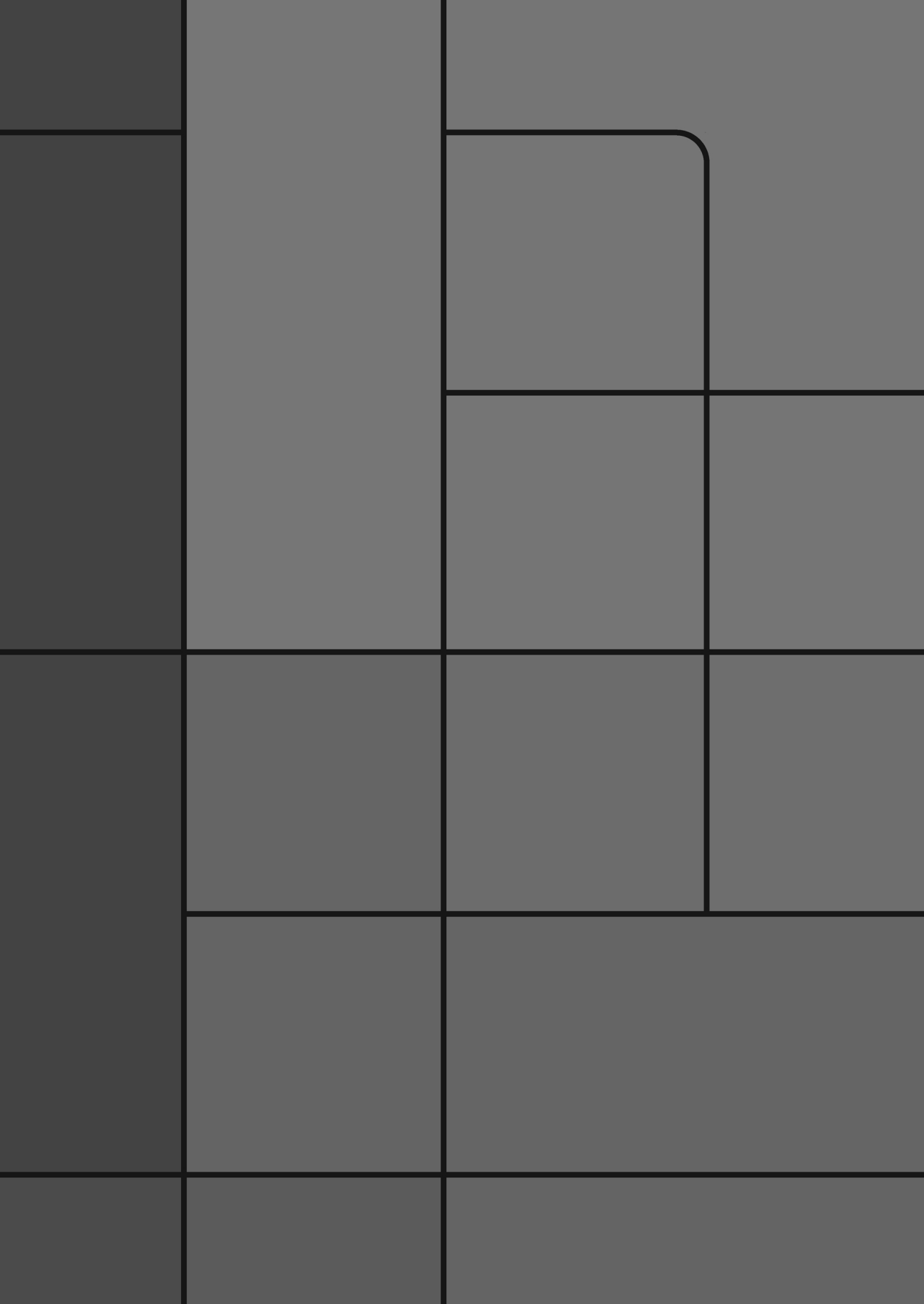


Figure 1. Flowchart
FU = Follow-up
UKA = Unicompartmental knee arthroplasty
TKA = Total knee arthroplasty
*Three patients did not undergo HTO due to patient's preference or clinician's choice to refrain from surgery

Supplementary table: Primary outcome (Sensitivity analysis)

	Brace (n=19)	**HTO (n=25)**	**Between group difference**
KOOS pain after 12 months	48.9 (44.3 to 53.5)	73.2 (68.2 to 78.2)	-35.5 (-20.9 to -51.0)

KOOS pain after 12 months was known for 48 of the 51 patients. Excluded from this sensitivity analysis were patients who did not undergo HTO (n=3), crossed over to HTO (n=1) or received TKA (n=3) before the 12 months' time point.
Data are presented as unstandardized predicted means and regression coefficients with 95% confidence interval in brackets KOOS = Knee Osteoarthritis Outcome Score KOOS pain was adjusted for age, sex, surgeon's experience and KOOS pain at baseline



Chapter 3

Longitudinal quantitative T2 mapping and SPECT-CT assessment of unloading therapy for medial knee osteoarthritis

Joost Verschueren, Dirk H.J. Poot, Mark V. van Outeren, Marcel Segbers, Eline M. van Es, Sita M. A. Bierma-Zeinstra, Max Reijman, Edwin H.G. Oei

Submitted

Abstract

Background and purpose

Quantitative imaging has great potential for early detection and monitoring effectiveness of potential therapies for osteoarthritis (OA). In this study, we explore whether T2 mapping and quantitative SPECT-CT can detect early changes in knee articular cartilage composition and subchondral bone turnover after unloading therapy with an unloader brace or a high tibial osteotomy (HTO) in patients with medial knee OA and varus knee malalignment. We also investigated correlations between these imaging modalities and with clinical outcomes.

Materials and methods

Patients 18-65 years were enrolled in a multicenter randomized controlled trial comparing an unloader brace to HTO. Patients were eligible if they had radiographic medial knee OA Kellgren & Lawrence (K&L) grade I-III and a varus knee malalignment. Magnetic Resonance Imaging with T2 mapping and SPECT-CT were conducted at baseline and after one year. We assessed differences in T2 relaxation times and maximum Standard Uptake Value (SUVmax) between baseline and follow-up scans and compared knee compartments at both time points. We assessed whether changes in imaging outcomes over time were correlated between the two techniques and whether these were correlated with clinical outcomes using the Knee Injury and Osteoarthritis Outcome Score (KOOS). Data were analyzed for the entire group and separately for each treatment arm.

Results

T2 relaxation times were statistically significantly increased in the lateral weight-bearing femoral and tibial regions at follow-up in the HTO group. The brace group showed statistically significantly increased T2 relaxation times of the medial weight-bearing femoral condyle. SUVmax values were statistically significantly decreased at follow-up in the medial compartment in the HTO group. No changes were observed in the brace group. The following findings applied to the entire study population as well as separated per treatment. Both techniques showed statistically significant outcomes between the medial and lateral compartments. No correlation was observed between the change in T2 values and the change in SUVmax over time. We did not observe a correlation between the change of the quantitative imaging outcomes and the change in clinical outcomes as reported by the KOOS questionnaire.

Conclusion

T2 mapping and SPECT-CT are able to detect changes after unloading therapy. These techniques depict OA processes and monitor OA therapies in a different and complementary way. Our results suggest that HTO accomplishes a load transfer from the medial to the lateral compartment, while the unloader brace does not. Change in T2 values or SUVmax does not correlate with clinical symptoms.

Keywords

Osteoarthritis; T2 mapping; SPECT-CT; Knee; Cartilage; Subchondral bone, Biomarker

Background and purpose

There is a growing interest in advanced quantitative imaging of osteoarthritis (OA) processes with the aim to diagnose and monitor OA in a more sensitive way that ideally also correlates well with clinical symptoms. T2 mapping is a widely applied quantitative MRI technique in OA research that is able to assess the collagen deterioration of articular cartilage.[88, 98, 160] Single Photon Emission Computed Tomography - Computed Tomography (SPECT-CT) visualizes subchondral bone remodeling with a nuclear tracer bound to a bisphosphonate that is absorbed in region of active bone turnover and thus accumulates in osteoarthritic joints.[93, 94] With the availability of advanced iterative reconstruction techniques in recent years, SPECT-CT can now be analyzed quantitatively.[161] We know that these quantitative imaging techniques are able to detect OA in an earlier stage as both articular cartilage deterioration and remodeling of the subchondral bone occur well before thinning of the cartilage or subchondral bone changes are visible on conventional radiography.[79, 162, 163] However, their use for the assessment of the effects of OA treatment have only been sparsely reported.[100-104]

In this study, we aim to explore whether T2 mapping and quantitative SPECT-CT are able to detect changes in knee articular cartilage and subchondral bone after unloading therapy with an unloader brace and a high tibial osteotomy (HTO) in patients with medial knee OA and a varus knee malalignment.[108, 109] Patients with medial knee OA that receive an unloading treatment for the medial compartment are a particularly interesting group for quantitative imaging research as both the unloaded affected knee compartment and the healthy compartment, that becomes more heavily loaded by the therapy, can be evaluated. We assess differences in quantitative imaging outcomes before and after initiation of the unloading treatment with an interval of one year and compare the medial and lateral knee compartments at both time points. We assess whether there is a correlation between the two imaging techniques in the observed changes over time. Finally, we examine the relationships between the longitudinal quantitative imaging results and clinical outcomes.

Materials and methods

Subjects and treatment

Patients were included in a multicenter randomized controlled trial (RCT) on the efficacy of a unloading brace versus an high tibial osteotomy treatment (trial number NTR NL4200).[Chapter 2] The study was approved by the institutional review board of the Erasmus MC University Medical Center Rotterdam (protocol number MEC-2013-492) and written informed consent was obtained from all participants. The inclusion criteria were: age 18-65 years, confirmed radiographic medial knee OA Kellgren & Lawrence (K&L) grade I-III and a varus knee malalignment of 0-14 degrees. Exclusion criteria were: lateral knee OA K&L grade ≥ II, knee flexion <100°, previous lateral meniscectomy and rheumatoid arthritis. When patients had bilateral knee complaints, the most symptomatic knee was included in the

study. Patients were included in 9 different hospitals in the Netherlands. All patients received an MRI scan with quantitative T2 mapping at time of inclusion and one year after the date of inclusion. SPECT-CT was only performed in patients that agreed to undergo this additional examination. In these patients, a scan was made on the same day as the MRI scan. All patients visited the Erasmus MC University Medical Center Rotterdam for the quantitative imaging, so both the MRI and SPECT-CT for both time points were made using the same imaging equipment. Patients filled in patient reported outcome measures (PROMs) at time of inclusion and one year later. For this study, we used the Knee Injury and Osteoarthritis Outcome Score (KOOS).[143, 164] The KOOS questionnaire consists of 5 subscales: 'symptoms', 'pain', 'activities of daily living', 'sport and recreation' and 'quality of life'. After the baseline scans and filling in the baseline PROMs, the patients were randomized to either a treatment with an unloader brace or a high tibial osteotomy. Patients were referred back to their attending orthopaedic surgeon for initiation of the treatment. The unloader brace (Unloader One, Össur hf., Reykjavík, Iceland) that was used is this study is an off-the-shelf brace available in different sizes that was individually fitted by a certified orthotist. The brace applies a valgus stress to the knee. It aims at shifting the load from the medial to the lateral knee compartment and thus unloading the osteoarthritic medial compartment. The HTO was performed according to the preferred surgical technique in the participating hospitals. This could either be a medial opening wedge or a lateral closing wedge osteotomy using a titanium plate and screws (TomoFix, DePuy Synthes, PA, USA), or a lateral closing wedge osteotomy using two cobalt-chrome staples (Stepped High Tibial Osteotomy Staples, Stryker, MI, USA). In both techniques, the varus malalignment of the knee is surgically adjusted to a 3 to 4 degrees valgus overcorrection.

Image acquisition

T2 mapping was performed on a 3 Tesla MRI scanner (Discovery MR750, GE Healthcare, Milwaukee, WI, USA) with a dedicated eight-channel transmit and receive knee coil (Invivo, Gainesville, FL, USA). The T2 mapping sequence was a 3D fast spin echo sequence with 5 echo times (3, 13, 27, 40, 68 ms); an in-plane resolution of 0.5x0.8 mm; and a 3 mm slice thickness.[165, 166] The scan time was 9:40 minutes. A 3D high spatial resolution fat-saturated fast spoiled gradient-echo (FSPGR) sequence was performed at baseline for cartilage segmentation as it provided a better contrast between the cartilage and the surrounding tissue than the T2 mapping scan. The SPECT-CT scan using two gamma cameras (Symbia T series; Siemens Healthcare, Erlangen, Germany) was made 3 hours after the administration of approximately 550 MBq 99mTc-HDP. A low-dose CT-scan of the knee was made directly after the SPECT acquisition. By registering the SPECT image to the CT scan, the disease activity was visualized at the correct anatomical location.

Image analysis

The T2 mapping scans were analyzed with an in-house developed MATLAB (R2021a; The MathWorks, Natick, MA, USA) software tool that uses Elastix to register the different images.[167, 168] Full-thickness femoral and tibial cartilage masks were segmented on the sagittal

slices of the FSPGR scan. Segmentation was conducted manually on five central slices of the medial and five central slices of the lateral compartment. The T2 mapping scans of both the baseline and the follow-up time points were registered to the FSPGR scan using rigid registration. Subsequently, T2 relaxation times in the segmented masks were calculated voxelwise (Figure 1). Femur and tibia were registered separate from each other to account for differences in knee flexion between the two scans.[167] A region of interest (ROI) analyses was defined by dividing the masks into a femoral weight-bearing, tibial weight-bearing and femoral posterior sub-region. The outer perimeters of the menisci delineated the weight-bearing ROIs of the femur and tibia. The femoral cartilage behind the posterior border of the menisci was considered the posterior femoral ROI. Weighted mean T2 relaxation times were calculated for each ROI, using the reciprocal square root of the Cramér-Rao lower bound as weight factor.[167]

The SPECT-CT scans were quantitatively reconstructed using Hermes Hybrid Recon (Version 1.1.2, Hermes Medical Solutions AB, Stockholm, Sweden) (Figure 1). Attenuation and Monte Carlo-based scatter correction were applied by means of a low-dose CT. Images were iteratively reconstructed using Ordered Subset Expectation Maximization with 5 iterations and 15 subsets. A 0.5 cm Gaussian post reconstruction filter was used. The reconstruction uses a predetermined calibration factor to enable quantification of the activity concentration in Bq/ml. Standard uptake values (SUV) were obtained by normalizing the activity concentration for net injected activity and patient weight. For the segmentation of the SPECT-CT scans, two 5 cm wide cubes were drawn. One in the medial knee compartment and one in the lateral. We chose not to define subregions for the femur and tibia and neither for the weight-bearing and posterior femoral compartment because of the limited resolution of the SPECT scan. It was difficult to specify whether activity around the joint line originated from the femur or the tibia. Care was taken to exclude activity from the osteotomy, the patellofemoral joint, the tibiofibular joint and the tibial tuberosity. In each region the SUVmax was measured, determined by the highest voxel value in the region.

Statistical analysis

A paired t-test was used to compare the differences in quantitative imaging outcomes between the baseline and follow-up scans of both knee compartments. The differences in quantitative imaging outcomes between both knee compartments at both time points were also assessed with a paired t-test. We used linear regression to examine the correlation between the change in T2 relaxation times and the change in SUVmax over time. We also used linear regression to examine the correlation between the changes in the quantitative imaging outcomes and the changes in clinical outcomes. For this analysis, we used the delta of the KOOS subscales as a dependent variable and delta of the T2 relaxation times or the SUVmax as an independent variable. The above mentioned analyses were performed for the whole group, but also separate for both treatment arms (unloader brace and high tibial osteotomy). We performed an independent t-test to assess whether there was a difference between the brace and HTO patients in T2 values or SUVmax change over time (a between

group comparison). In case of crossovers in treatment, we analyzed patients in the group of the treatment they received by the time of the follow-up measurements (an as treated analyses). A two-sided p-value of less than 0.05 was considered statistically significant. Statistical analysis was performed using SPSS (IBM SPSS Statistics for Windows, Version 28.0.1.0 Armonk, NY, USA).

Results

Population characteristics are described in Table 1. Fifty-one patients were included in the RCT. Figure 1 shows a flowchart of the available scans per treatment arm at both time points. All patients filled out the baseline PROMs. One patient was allocated to the brace treatment arm, but received an HTO after 7 months because of unsatisfactory results of the brace treatment. Twelve patients were not available for the follow-up quantitative imaging. Three patients received an unilateral or total knee arthroplasty before the follow-up measurements. One patient was allocated to the HTO treatment, but was excluded for this treatment by the attending surgeon because of significant patellofemoral OA on the SPECT-CT scan. This patient was excluded from the follow-up analysis because no unloading treatment was given. Two other patients refrained from the HTO therapy after randomization and did not respond to the invitation for follow-up measurements. Four patients started their treatment but did not respond to the invitation for follow-up measurements or did not want to travel to the hospital for these measurements. All patients that received the follow-up MRI and SPECT-CT scans also completed the clinical questionnaires.

The analyses of the follow-up T2 mapping scan in patients that underwent an HTO resulted in some problems because of the implanted material (Figure 2). In multiple patients, it caused visual distortion of the cartilage in certain ROIs or resulted in registration errors. In 13 patients, at least one cartilage ROI was not available for analyses due to visual distortion by the metal induced artifacts. In 16 patients, one or more cartilage ROIs had to be segmented manually due to registration errors. The above mentioned problems mainly occurred in the tibial ROIs. We previous showed that reliable T2 values can be obtained from cartilage ROI in the vicinity of HTO material as long as the cartilage is not visually distorted.[169] In four patients the implanted osteotomy material was removed before the follow-up scan. There were no issues with the follow-up analyses of the patients that received brace treatment.

T2 mapping

In Table 2, the average T2 relaxation times are shown for all patients, as well as separated per treatment arm. In general, there was an increase in the T2 values at the follow-up measurement compared to the baseline scan. The whole group showed a statistically significant increase in T2 values in all weight-bearing regions except for the medial tibial plateau. When the results were separated per treatment arm, the statistically significant increase of the lateral weight-bearing regions was only observed in the HTO group. In this

group, the T2 values of the medial compartment did not statistically significantly change over time. On the other hand, the brace group showed a statistically significant increase of the medial weight-bearing femoral condyle, while the cartilage of the lateral compartment did not change significantly. When comparing the medial and lateral ROIs of the baseline scan, we observed statistically significant higher medial weight-bearing T2 values compared to the lateral ROIs of both the femur and the tibia for both the group as a whole and separated per treatment. The follow-up scans also showed higher T2 values in the medial weight-bearing ROIs, but there was only a statistically significant difference in the total group of patients and in the tibial plateaus of the brace group. The posterior femoral condyle cartilage did not show any statistically significant differences, neither between baseline and follow-up, nor between medial and lateral. Comparison of the change in T2 relaxation times between the brace and HTO group did not show any statistically significant differences in any of the cartilage ROIs.

SPECT-CT

In table 3, the average SUVmax values are shown for all patients, as well as separated per treatment arm. In the comparison between the baseline and follow-up scans, we observed a statistically significant decrease in SUVmax in the medial compartment. When comparing the two treatment arms, this statistically significant decrease in the medial compartment was only seen in the HTO group. No statistically significant changes in SPECT activity of the lateral compartment were seen between baseline and follow-up in all groups. The SUVmax values of the medial compartment were statistically significant higher than the lateral compartment in both the baseline and follow-up scans for both the group as a whole and separated per treatment. Comparison of the change in SUVmax between the brace and HTO group did not show any statistically significant differences for both the medial and the lateral compartment.

Correlation of change in T2 and SUV

We did not observe a correlation between both imaging modalities in any of the ROIs. This applied for both the group as a whole and separated per treatment.

Correlation of change in quantitative imaging and clinical symptoms

We did not observe a correlation between the quantitative imaging outcomes of the T2 mapping or SPECT-CT and the clinical outcomes as reported in the KOOS questionnaire for all ROIs and all KOOS subscales (data not shown).

Discussion

The results of this explorative study using quantitative T2 mapping and SPECT-CT in a multicenter RCT on the effects of unloading therapy for medial knee OA show that both techniques are clearly able to differentiate between regions with severe and less severe OA. The statistically significant different T2 values of the medial and lateral weight-bearing ROIs indicate that, besides cartilage loss, the remaining cartilage also has a different, deteriorated, composition, which is in in accordance with previous research.[88, 160, 170] The SPECT-CT results support the concept that OA causes changes to the subchondral bone as a separate phenomenon from the cartilage changes in the osteoarthritis process.[94, 171] The changes in T2 relaxation times and SUVmax over time show clear differences between both unloading therapies. The results suggest that HTO effectively transfers load from medial to lateral compartment, as evidenced by increased lateral T2 values and decreased medial SUVmax, unlike the brace group. These results are in line with the results of the clinical outcomes of this RCT showing that patients receiving an HTO improve clinically based on the PROMs after 1 year of follow-up while the brace group shows almost no improvement.[Chapter 2] Only limited literature has been published on longitudinal quantitative imaging assessment of OA unloading therapies.[100] A study using T1rho and T2 mapping to evaluate the effect of a medial opening wedge HTO using temporarily fixation with an external fixator (hemicallotasis) on the medial weight-bearing femoral and tibial cartilage showed a significant decrease in T2 values one year after surgery, corresponding to an improvement of the cartilage. No significant differences were observed in the T1rho results. This study did, however, not examine the effects of the HTO on the lateral cartilage. Another study using delayed Gadolium Enhanced MRI of Cartilage (dGEMRIC) in the assessment of the effects of HTO and knee distraction did not show statistically significant changes in cartilage quality two years after knee distraction.[104] On the other hand, the dGEMRIC values two years after an HTO showed lower proteoglycan concentration in medial cartilage (associated with poorer quality) and higher concentration in lateral cartilage. These contradictory findings were attributed to the idea that the proteglycan concentration also depends on the pressure on the cartilage, which is changed after HTO, resulting in increased lateral compression and a slight medial decompression. A previous study in which SPECT-CT was performed before and after a medial opening wedge HTO showed a reduction of bone tracer uptake in the medial compartment.[172] This study, however, did not perform a quantitative assessment of these findings.

We did not observe any correlation between the change in T2 values and the change in SUVmax in any of the ROIs. A possible explanation is that, although both techniques show the consequences of load transfer in the HTO group, they depict it in a different way. T2 mapping shows increased deterioration of the lateral compartment, while quantitative SPECT-CT shows an decrease in disease activity of the medial compartment after HTO treatment. There was, however, also no correlation between the change of the T2 values of the lateral weight-bearing ROIs and the change in SUVmax of the medial compartment in

HTO group. We did not observe a correlation between the change of the quantitative imaging outcomes and the change in clinical outcomes, as reported in the KOOS questionnaire. Although somewhat disappointing, this was not unexpected, as to date no imaging technique has displayed a distinct correlation with the severity of the clinical OA symptoms.

As illustrated in this paper, T2 mapping and quantitative SPECT-CT assess different aspects of the OA process. T2 mapping provides a measure for early structural damage, while SPECT-CT offers compelling insights into OA by revealing the current metabolic activity of the disease. This makes both techniques complementary in OA research. When implementing these techniques in clinical research of clinical practice, they have their advantages and disadvantages. The advantage of T2 mapping over SPECT is that it does not require an intravenous agent, there is no waiting time between injection and scanning, and the spatial resolution is higher. Furthermore, when a SPECT-CT scan is made shortly after performing the osteotomy, there will be substantial activity resulting from the osteotomy that might interfere with the measurement of the OA process. On the other hand, SPECT-CT is not affected by artifacts caused by the implanted metal in an HTO procedure. Our study also showed relatively greater quantitative differences between the affected and unaffected compartment with SPECT-CT. This might suggest that SPECT-CT is more sensitive than T2 mapping for capturing subtle changes, but this is not supported by our longitudinal data.

A strength of this unique study is the comprehensive assessment of OA interventions using of multimodal quantitative imaging techniques. The study also has limitations. First, we studied a small sample size with a skewed distribution between the patients that received the brace and patients that received the HTO treatment. The skewed distribution was primarily due to our choice for block randomization. Initially, 124 people were to participate in the study, which was taken into account in the block randomization. Additionally, stratification was performed in the randomization for all the nine centers that participated in the RCT. Due to slow inclusion, an interim analysis was executed which justified a reduced number of inclusions based on the primary clinical outcomes. Therefore, the study was concluded after 51 patients. This resulted in the small sample size and the skewed distribution. There was an even larger mismatch between the treatment arms in the patients that received an SPECT-CT scan, because this scan was not performed in every patient. Because of the limited sample size, we did not perform sub-analyses for the different osteotomy techniques. Another limitation is that in nine patients, we did not obtain a follow-up MRI and SPECT-CT scan. The fact that the imaging was done at one location, while patients were included in different centers across the country, meant that some of these patients did not want to travel for the follow-up scans. We chose to perform all scans at one location as quantitative imaging results can vary between different scanning protocols and vendors and therefore cannot be pooled.[173] This emphasizes the need for standardization in using quantitative imaging in multicenter studies.[79] An additional limitation was the time lag between the moment of inclusion and the start of therapy, especially in HTO. As a result, the time between intervention and follow-up scan was relatively short. However, we believe that

the outcome of the difference between brace and HTO would not be different if the therapy had been performed sooner after randomization. The disparities discovered might have been even more significant had the therapies been given more time to take effect. We had one protocol violation in the study as a patient was excluded from unloading therapy because of significant patellofemoral OA on the SPECT-CT scan. This scan was not part of the regular work-up for medial knee OA, so the attending surgeon normally does not have this information. However, the scan could not be anonymized for safety reasons. This allowed the surgeon to view the results of the scan and decided to forego the unloading therapy. There was one treatment crossover during the course of the study. One patient that was randomized to the brace group but received an HTO 7 months after inclusion. This was allowed according to the study protocol. Since we assumed that the influence of the treatment on the structural properties of cartilage and bone has no subjective component, we decided to analyze this patient in the HTO group (as treated analyzes). A final limitation is that the RCT was not powered for the T2 mapping or SPECT-CT outcomes, which has to be taken into consideration when interpreting the results of the statistical tests.

In conclusion, both T2 mapping and quantitative SPECT-CT show clear differences between the medial and lateral compartment of patients with medial knee OA and are able to detect changes of an unloading therapy after a relative short period of time of only one year. Both techniques depict the OA processes in a different way and are therefore useful and complementary for monitoring OA therapies.

Tables

Table 1. Baseline characteristics of the study population

	Brace	**HTO**
Patients, n	23	28
Male, n (%)	14 (61)	17 (61)
Age, years	50.0 (±6.8)	55.3 (±6.6)
BMI, kg/m^2	29.0 (±4.1)	29.8 (±4.3)
Knee varus, degrees	6.7 (±3.1)	5.7 (±2.3)
Days between inclusion and start treatment	24 (±18)	74 (±60)

Data is presented as mean with standard deviation between parentheses, or reported otherwise.

Table 2. T2 mapping results

All patients	**T2 relaxation times**				**p-values**			
	Baseline		**Follow-up**		**Medial vs. lateral**		**Baseline vs. follow-up**	
	Medial	**Lateral**	**Medial**	**Lateral**	**Baseline**	**Follow-up**	**Medial**	**Lateral**
Weight bearing femoral condyle	44.2 (41.3 - 47.1)	38.3 (37.4 - 39.2)	44.3 (41.2 - 47.3)	39.9 (38.2- 41.2)	0.00	0.02	0.01	0.05
Posterior femoral condyle	39.1 (37.9 - 40.2)	38.6 (37.4 - 39.8)	38.1 (36.8 - 39.4)	37.6 (36.1 - 39.1)	0.56	0.58	0.27	0.54
Weight bearing tibial plateau	40.9 (39.3 - 42.6)	34.8 (33.8 - 35.9)	40.5 (38.1 - 42.9)	37.3 (35.5 - 39.1)	0.00	0.04	0.43	0.00
Brace	**T2 relaxation times**				**p-values**			
	Baseline		Follow-up		Medial vs. lateral		Baseline vs. follow-up	
	Medial	Lateral	Medial	Lateral	Baseline	Follow-up	Medial	Lateral
Weight bearing femoral condyle	42.5 (38.5 - 46.5)	38.2 (36.7 - 39.8)	44.1 (38.7 - 49.5)	38.9 (37.1 - 40.7)	0.03	0.06	0.03	0.50
Posterior femoral condyle	39.5 (37.5 - 41.4)	37.6 (36.3 - 38.9)	37.2 (35.4 - 39.0)	37.0 (34.6 - 39.4)	0.06	0.85	0.19	0.60
Weight bearing tibial plateau	40.2 (37.0 - 43.3)	34.4 (32.7 - 36.1)	39.5 (35.9 - 43.2)	35.5 (33.2 - 37.8)	0.00	0.05	0.78	0.39

Table 2. Continued

HTO	T2 relaxation times				p-values			
	Baseline		Follow-up		Medial vs. lateral		Baseline vs. follow-up	
	Medial	Lateral	Medial	Lateral	Baseline	Follow-up	Medial	Lateral
Weight bearing femoral condyle	45.6 (41.4 - 49.8)	38.4 (37.3 - 39.4)	44.4 (41.3 - 47.6)	40.4 (37.9 – 43.0)	0.00	0.21	0.15	0.05
Posterior femoral condyle	38.7 (37.3 - 40.2)	39.4 (37.4 - 41.5)	38.9 (37.0 - 40.8)	38.2 (36.1 - 40.3)	0.54	0.40	0.88	0.73
Weight bearing tibial plateau	41.6 (39.8 - 43.4)	35.2 (33.8 - 36.6)	42.1 (39.8 - 44.4)	39.2 (36.5 - 41.9)	0.00	0.64	0.44	0.00

Data is presented as mean with 95% CI between parentheses.. The means displayed are of all the patients in the specified groups. These are not necessarily the means used in the t-tests, because for these tests only complete cases were used. Besides the lost to follow-up, in 13 patients of the HTO group at least one cartilage ROI was not available for analyzes due to visual distortion by metal induced artifacts in the follow-up scan. This problem mainly occurred in the tibial ROIs. In baseline vs. follow-up comparison for the HTO group, the number of complete cases ranged from 8 to 19 depending on the ROI.

Table 3. SPECT-CT results

SPECT-CT	SUVmax				p-values			
	Baseline		Follow-up		Medial vs. lateral		Baseline vs. follow-up	
	Medial	Lateral	Medial	Lateral	Baseline	Follow-up	Medial	Lateral
All patients	13.6 (10.3 - 16.9)	7.1 (5.5 - 8.7)	12.0 (9.2 - 14.9)	7.2 (6.0 - 8.4)	<.001	0.00	0.05	0.89
Brace	13.8 (9.0 - 18.7)	6.6 (3.9 - 9.2)	14.4 (7.0 - 21.8)	6.4 (3.7 - 9.0)	0.01	0.02	1.00	0.82
HTO	13.4 (8.7 - 18.2)	7.4 (5.2 - 9.5)	11.0 (7.7 - 14.3)	7.6 (6.0 - 9.1)	0.01	0.04	0.03	0.94

Data is presented as mean with 95% CI between parentheses. The means displayed are of all the patients in the specified groups. These are not necessarily the means used in the t-tests, because for these tests only complete cases were used.

Figures

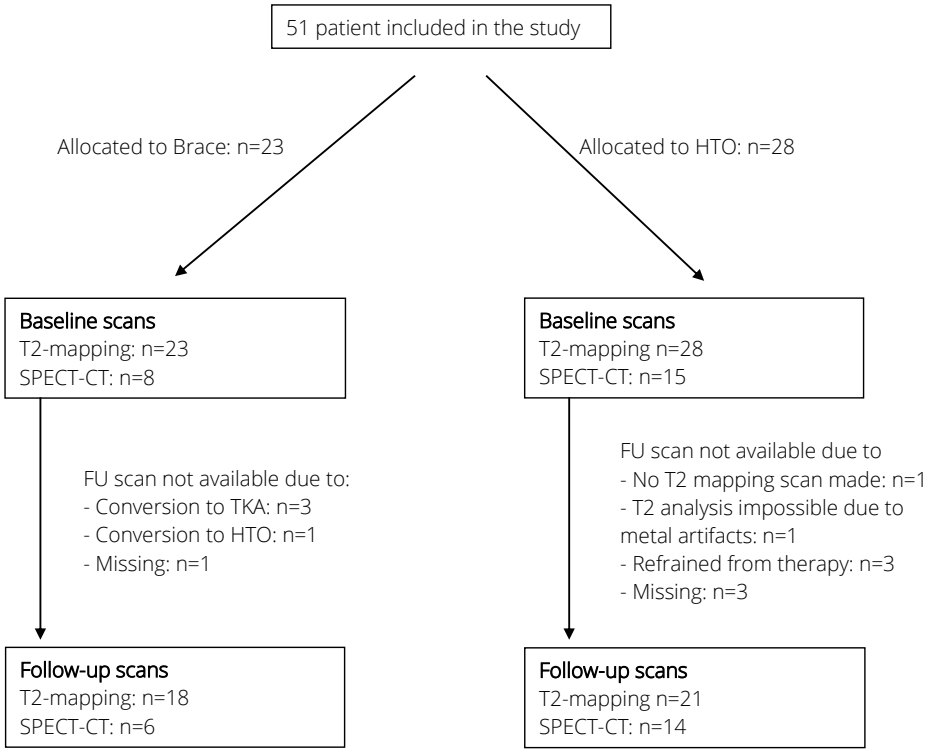


Figure 1. Flowchart of the available quantitative imaging scans per treatment arm at both time points

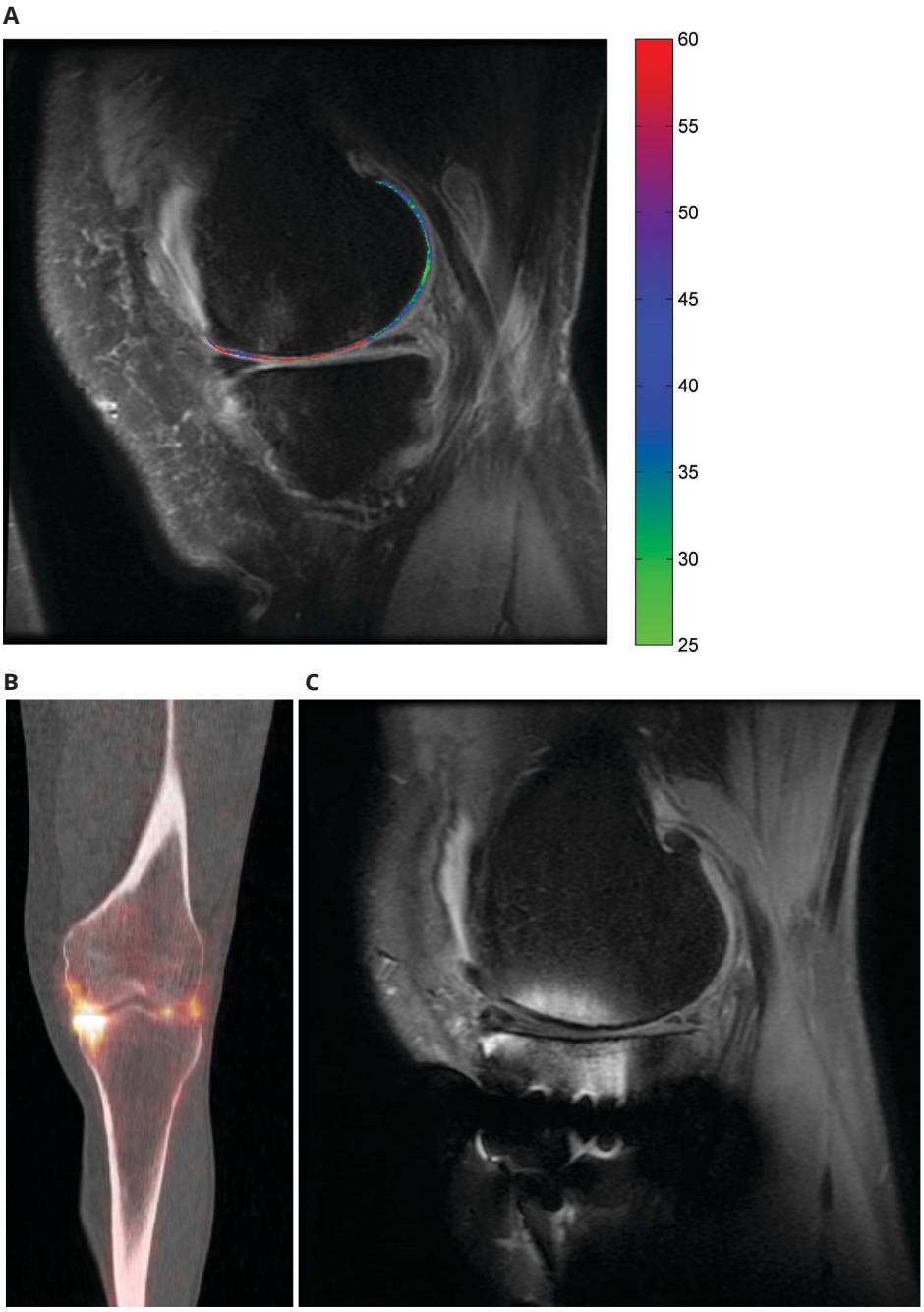
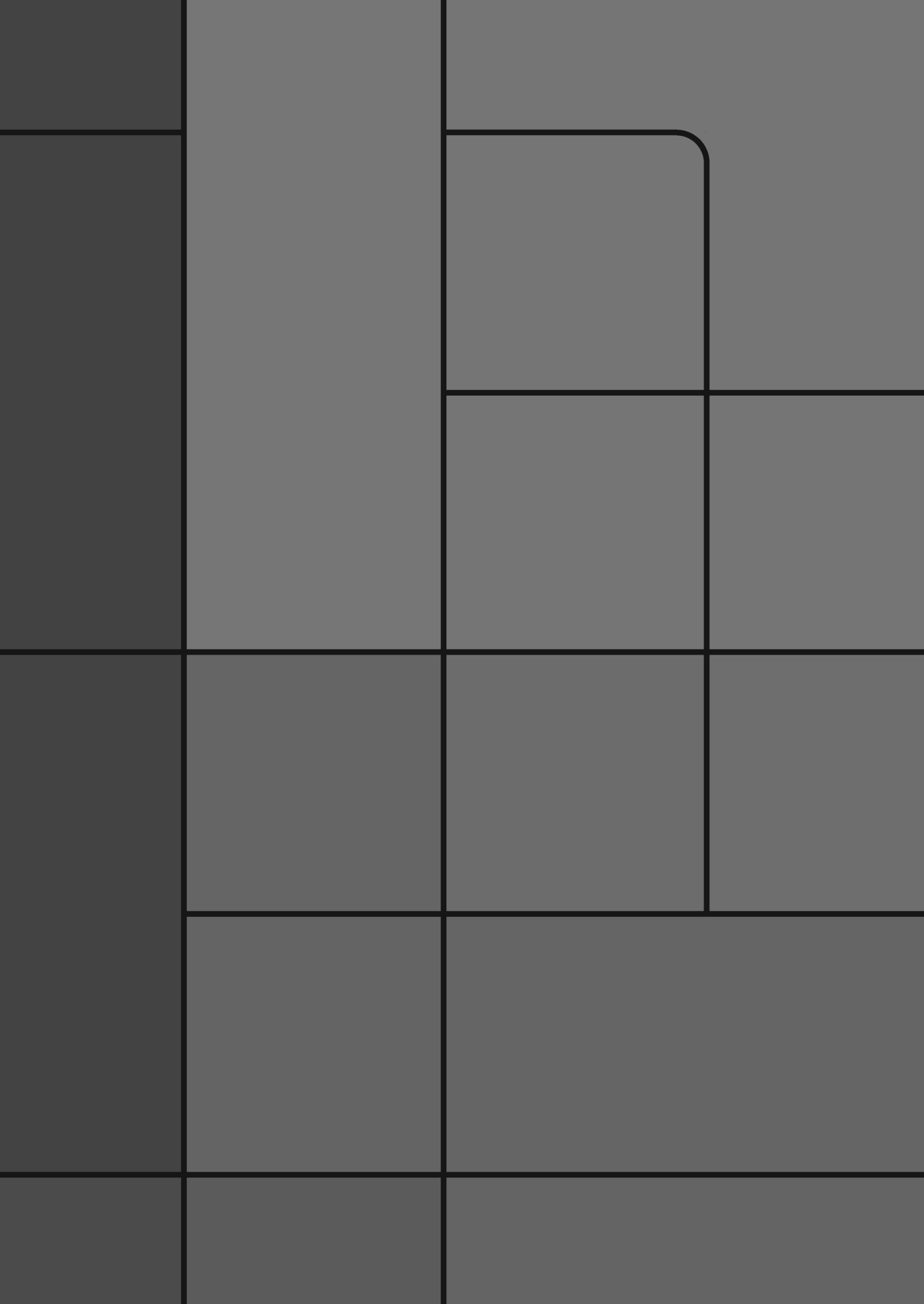


Figure 2. A. Sagittal T2 map of medial femoral condyle. Higher T2 relaxation times (in milliseconds) represent a more deteriorated condition of the cartilage. **B.** Coronal SPECT-CT image showing high activity in the medial compartment (left side of the image). **C.** Sagittal T2 image of the medial compartment after an HTO showing artefacts caused by the implanted material.



Chapter 4

T2 relaxation times of knee cartilage in 109 patients with knee pain and its association with disease characteristics

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Abstract

Background and purpose

Quantitative T2 mapping MRI of cartilage has proven value for the assessment of early osteoarthritis changes in research. We evaluated knee cartilage T2 relaxation times in a clinical population with knee complaints and its association with patients and disease characteristics and clinical symptoms.

Patients and methods

In this cross-sectional study, T2 mapping knee scans of 109 patients with knee pain who were referred for an MRI by an orthopedic surgeon were collected. T2 relaxation times were calculated in 6 femoral and tibial regions of interest of full thickness tibiofemoral cartilage. Its associations with age, sex, BMI, duration of complaints, disease onset (acute/chronic) and clinical symptoms were assessed with multivariate regression analysis. Subgroups were created of patients with abnormalities expected to cause predominantly medial or lateral tibiofemoral cartilage changes.

Results

T2 mapping data was collected of 109 patients. T2 relaxation times statistically significantly increased with higher age and BMI. In patients with expected medial cartilage damage, the medial femoral T2 values were significantly higher than the lateral, in patients with expected lateral cartilage damage the lateral tibial T2 values were significantly higher. A traumatic onset of knee complaints was associated with an acute elevation. No significant association was found with clinical symptoms.

Interpretation

Our study demonstrates age, BMI and type of injury dependent T2 relaxation times and emphasize the importance of acknowledging these variations when performing T2 mapping in a clinical population.

Introduction

Knee osteoarthritis (OA) is currently mainly diagnosed on clinical presentation.[1] Conventional radiography depicts morphological articular cartilage changes indirectly and is insensitive to both early-stage OA and subtle progression of the disease.[68] MRI is able to visualize articular cartilage directly and is therefore more sensitive to osteoarthritic changes.[174] But, similar to conventional radiography, conventional MRI relies primarily on the identification of morphological changes in damaged knee cartilage and is also limited to depicting relatively advanced signs of degeneration.[175] In the last 2 decades, innovative quantitative methods of MRI have been developed that have the potential to measure articular cartilage degeneration prior to morphological cartilage damage and, thus, might be able to identify cartilage at risk of developing irreversible cartilage damage.[82] A well-validated and quantitative MRI technique, transverse relaxation time (T2) mapping, is regarded as the best technique to determine the hydration content, collagen fiber orientation, and collagen network integrity in articular cartilage.[88] These cartilage properties are known to be altered in the initial stages of OA development.[176] T2 mapping is expressed in T2 relaxation times, which tend to increase with more advanced stages of cartilage damage.[170] The technique is widely used in scientific studies such as the Osteoarthritis Initiative (OAI).[177] However, as current T2 mapping data is gathered in research settings with clear inclusion criteria based on age, sex, type of knee disorder, and OA stage, these results cannot directly be generalized to clinical practice.[177] Therefore, we assessed the association of T2 relaxation times of knee articular cartilage with patient and disease characteristics and clinical symptoms in an unselected routine clinical population of patients with knee complaints.

Patients and methods

In a period of 18 months, all patients with complaints of knee pain referred for MRI of the knee by an orthopedic surgeon (JLD) from Stanford University Medical Center were eligible for the study.

Image acquisition

The patients were scanned on a 3.0 Tesla (T) MRI scanner (MR 750, GE Healthcare, Milwaukee, WI, USA) with a flexible 16-channel receive-only coil (NeoCoil, Pewaukee, WI, USA). The patient's knee was fixed with a leg holder in slight flexion to position the coil and reduce motion artifacts. In addition to a routine clinical knee MR protocol used by the radiologist to assess structural changes in the knee, a 3D fast spin echo T2 mapping sequence was added to the protocol during the trial period. This sequence with variable refocusing flip angle schedules uses T2 magnetization preparation followed by pseudo steady-state 3D FSE acquisition.[166, 178] The main T2 mapping sequence parameters were: 5 echo times (6, 12, 25, 38, 64 ms); 3 mm slice thickness; an in-plane resolution of 0.5 x 0.8 mm; and a scan time of approximately 6 minutes.

Image analysis

The T2 mapping images were analyzed using an in-house developed MATLAB software tool.[167] Full-thickness tibiofemoral cartilage masks were segmented on 6 slices (3 central slices of the medial and 3 central slices of the lateral compartment, respectively) of a sagittal T2 weighted sequence, which was part of the routine MR protocol (Figure 1). We used this sequence for segmentation because of better contrast between the cartilage and the surrounding tissue. The T2 mapping scan was subsequently registered to the T2 weighted scan using rigid registration to calculate T2 relaxation times in the segmented masks. The masks were further divided into a femoral weight-bearing, tibial weight-bearing, and femoral posterior region of interest (ROI) for both the medial and lateral knee compartment. The outer perimeters of the menisci demarcated the weight-bearing ROIs of the femur and tibia. The posterior ROIs contained the femoral cartilage behind the posterior border of the menisci. The 6 ROIs were also combined to calculate an average tibiofemoral T2 relaxation time for each knee.

Patient and disease analysis

Patient characteristics (age, sex, and BMI), disease characteristics (diagnosis, duration of complaints, and onset of disease), and clinical symptoms were retrospectively collected through the electronic patient record. Diagnosis was based on the surgical report (when available), clinical report, and MRI report. The surgical report was considered the reference in case of discrepancies between the reports. The duration of complaints, defined as the period between the onset of knee pain and the date of the MRI, was divided into acute (< 1 month), subacute (1-6 months) and chronic (> 6 months). The onset of disease was specified as traumatic versus non-traumatic. To assess clinical symptoms, the Knee Injury and Osteoarthritis Outcome Score (KOOS) questionnaire was recorded for patients on their first visit to the Outpatient Clinic.[164] In addition to the KOOS subscale ("symptoms", "pain", "activities of daily living", "sport and recreation", "quality of life") scores, all 42 items of the KOOS were dichotomized into absence versus presence of knee complaints. When patients scored zero (i.e., no complaints), the complaint was considered absent, while a score of 1 to 4 indicated presence of the complaint. The KOOS questionnaire was disregarded when it was filled in more than 6 months before the MRI.

Statistics

Statistical analysis was performed using SPSS (IBM SPSS Statistics for Windows, Version 21.0; IBM Corp, Armonk, NY, USA). Associations between T2 relaxation times and patient characteristics, disease characteristics, and clinical symptoms were tested using linear regression models. T2 relaxation times were used as dependent variable and patient characteristics, disease characteristics, and clinical symptoms as independent variables. We performed both univariate and multivariate analyses. Subgroups were created of patients with abnormalities expected to cause predominantly isolated medial (medial meniscal tear, medial bone marrow edema, or medial focal cartilage/osteochondral damage/degeneration) or lateral tibiofemoral cartilage changes (lateral meniscal tear, lateral bone marrow edema,

or lateral focal cartilage/osteochondral damage/degeneration).[179, 180] When patients had abnormalities in both compartments of the knee, they were not included in the subgroups. Differences between the medial and lateral ROIs were tested with a paired t-test. Multiple imputations analysis was used for missing data. A p-value of less than 0.05 was considered statistically significant.

Ethics, funding, data sharing, and potential conflicts of interest

The study was approved by the institutional review board of Stanford University Medical Center (protocol number 26840). Informed consent was obtained from all participants. This research was not supported by grants from any funding agency in the public, commercial, or not-for-profit sectors. The dataset that is necessary to replicate main findings can be obtained from the authors upon reasonable request. GEG and EHGO receive research support from GE Healthcare. The study was performed during the visiting professorship of EHGO at Stanford University Medical Center, which was partially funded by the Dutch Arthritis Foundation.

Results

146 patients met the inclusion criteria of whom 109 were eligible for further analyses (Table 1). Main reasons for exclusion were no T2 mapping scan undertaken or insufficient quality of this scan due to metal and movement artifacts, which occurred relatively frequently because a surface coil was used instead of a dedicated knee coil. In 8 patients both knees were scanned. The most troublesome knee was included for analysis. The KOOS questionnaire was available for 55 subjects, as not all participants filled in the questionnaire at their first visit to the orthopedic surgeon. 8 questionnaires were disregarded because of the time interval with the MRI scan. No statistically significant differences were found in patient and disease characteristics between the patients with and without a KOOS questionnaire (data not reported).

Patient characteristics

Data on BMI was missing for 3 patients. In the multivariate analysis with age, sex, and BMI as independent variables, age showed a statistically significant association with T2 relaxation times in all medial ROIs and the lateral weight-bearing tibial ROI, as well as the total tibiofemoral cartilage (Table 2). Increasing T2 relaxation times were seen with higher age. BMI showed a significant association with the total tibiofemoral cartilage. In the ROI analyses, only a significant association was seen in the lateral weight-bearing tibial cartilage. Sex did not seem to have an effect on T2 relaxation times. Figure 2 shows the scatter plots

of age and BMI, respectively, with T2 relaxation times of the total tibiofemoral cartilage with the corresponding trend lines based on the (univariate) Pearson correlation coefficients.

Disease characteristics

We identified 35 patients with abnormalities that are likely the cause of medial cartilage damage. The medial femoral ROIs showed statistically significantly higher T2 relaxation times compared with the lateral femoral ROIs (Table 3). 21 patients were expected to have predominantly lateral cartilage damage. Statistically significantly higher T2 values were seen only in the lateral weight-bearing tibial ROI.

A trend towards decreased cartilage T2 values with an increase in duration of complaints was observed (Figure 3). However, this association was not statistically significant when the analysis was adjusted for age, sex, and BMI. In the case of a traumatic onset of knee pain, T2 relaxation times were the highest in patients with the shortest time between the onset and MRI acquisition. There was a gradual decline in T2 relaxation times between the MRIs undertaken in < 1 month, 1-6 months and > 6 months after a traumatic onset. In patients with a non-traumatic onset of knee pain, T2 relaxation times appeared to be stable between the time points (Figure 3). These trends were seen for both the total tibiofemoral cartilage and the specific ROIs.

Clinical symptoms

Mean KOOS values and standard deviations per subscale are displayed in Table 1. Univariate analyses showed a statistically significant association between clinical symptoms and total tibiofemoral T2 relaxation times for 2 of the 5 KOOS subscales (Pain: $p = 0.02$; Activities of daily living: $p = 0.02$). A lower score, i.e., more complaints, on the KOOS questionnaire was associated with elevated T2 relaxation times. When correcting for age, BMI, and sex, none of the associations remained significant. The item-specific analysis of the KOOS questionnaire revealed that, after adjusting for age, sex, and BMI, only "difficulties with descending stairs" was statistically significantly associated with elevated total tibiofemoral T2 relaxation times. Multivariate ROI-specific analysis did not show statistically significant associations with the different KOOS subscales either.

Discussion

In this study, we assessed the association of T2 relaxation times of the tibiofemoral knee cartilage with patient and disease characteristics and clinical symptoms in an unselected clinical population of 109 patients. A positive statistically significant association was observed between T2 relaxation times and age and BMI, while sex did not have an effect on T2 relaxation times. Age seemed to have an overall effect on T2 values as increasing T2 values with increasing age were seen in most ROIs. Increasing T2 relaxation times with aging and higher BMI have previously been described in patients over 45 years old.[177] Furthermore,

Mosher et al. found increasing T2 relaxation times in asymptomatic woman older than 45 compared with below 45 years.[181] Our data shows these associations are seen in the whole adult range of age. BMI showed a trend towards increasing T2 values with increasing BMI, but a significant association was seen only in the lateral tibial weight-bearing cartilage. This is in contradiction to the findings of a recent paper that found an association between obesity and the risk of developing medial tibiofemoral OA.[182] The range of T2 values in our study was between 35 and 50 ms, as can be seen in the scattorplots, which is in line with previously reported values.[88] The increase in T2 relaxation time per unit of age or BMI was small, but this is what can be expected considering a difference of only 15 ms between the highest and lowest values. As most studies using T2 mapping focus on more advanced disease in selected patient groups, it is not surprising that larger differences in T2 values between damaged and healthy cartilage are found. We found no effect of sex on T2 relaxation times for both the total population and the age-dependent subgroups. A previously performed study looking at the influence of sex on T2 relaxation times also did not find such effect, but that study was based on a small and young population aged between 22 and 29 years.[183] Other previous research showed only a weak association between T2 relaxation times and sex in the OAI population (age 45-65) without signs of radiographic OA.[177]

Differences in T2 values between medial and lateral compartments were found in patients with unicompartmental abnormalities. Previous studies with strict inclusion criteria already showed increasing T2 relaxation time in the medial knee compartment in patients with meniscal tears and in the lateral knee compartment in patients with anterior cruciate ligament injuries.[184, 185] Our study confirms this effect in a heterogeneous population. We found statistically significantly higher T2 values in the medial femoral ROIs in patients with abnormalities expected to cause predominantly medial cartilage changes. In patients with suspected isolated lateral cartilage changes, a statistically significant difference was found only in the tibial ROIs. Just like the correlations of age and BMI with T2 relaxation times, it is remarkable that higher medial femoral cartilage T2 values were associated with increasing age and medial abnormalities and higher lateral tibial values were associated with increasing BMI and lateral abnormalities. It would be interesting to assess the influence of mechanical leg axis on these findings, but as long leg radiographs were not available, it was not possible to answer this question.

Duration of complaints could potentially lead to transient variation of T2 relaxation times within patients as evidence is provided that the integrity of the cartilage collagen network is compromised soon after joint injury.[186] Our study revealed higher T2 relaxation times in patients who had an interval of less than 1 month between trauma and MRI compared with patients with an interval longer than 6 months. However, since we did not perform follow-up measurements of the same patient, no conclusions regarding the trend over time of T2 relaxation time following trauma can be made based on our data. Nonetheless, it is worth noting that in the case of non-traumatic knee pain the duration of complaints did not cause variation in T2 relaxation times.

As far as we know, no imaging modality has shown a good correlation with clinical symptoms of knee injury and osteoarthritis in an unselected routine clinical population. In our study, significant associations were found between T2 values and two domains of the KOOS questionnaire in the univariate analysis. However, this finding was not sustained when corrected for age, sex, and BMI, with age being the predominant covariate. When looking at the item-specific analysis, we found only "any difficulty with descending stairs" to be correlated with T2 relaxation times after correction. Although a large set of symptoms was tested, and based on repeated testing coincidental findings are possible, previous studies also reported difficulties with climbing stairs to be a sensitive and prodromal symptom in osteoarthritis.[187, 188] The wide range in age and the known increase in knee complaints with age might be responsible for the absence of further associations between T2 relaxation times and clinical symptoms in our study.[189]

Our study has several limitations. By using a clinical orthopedic population, we included patients with a wide range in age, BMI, diagnoses, and clinical symptoms. The combination of this heterogeneity and limited sample size could explain the absence of clear associations between T2 values and disease characteristics and clinical symptoms in our study. A second limitation is that we had a valid KOOS questionnaire available for only half of the patients. It was common practice at the Orthopedic Outpatient Department to ask patients to fill in the questionnaire. Unfortunately, this was not strictly controlled. We are aware that previous studies have shown T2 differences between superficial and deep cartilage layers.[183, 190] However, as our T2 mapping sequence is a 3D sequence with coverage of the whole knee, we considered the spatial resolution not good enough to perform these subregional analyses. Finally, we realize the magic angle effect could influence T2 values. However, as all patients were positioned in a standardized fashion, the effect would be similar for all patients. Together with the type of analyses we performed, we do not think the magic angle effect substantially influenced our results.

To date, the application of T2 mapping is primarily in clinical research with patient groups based on well-defined inclusion criteria. In contrast to the success of T2 mapping in research trials like the OAI, the poor associations of T2 mapping with patient and disease characteristics observed in our study illustrate the difficulties of implementing such a quantitative MR technique in a routine clinical population. In conclusion, our results emphasize the importance of acknowledging patient and disease characteristics when performing T2 mapping in a clinical population.

Tables

Table 1. Population characteristics

Patient characteristics	
Male, n (%)	62 (57)
Age, years (SD, range)	41.1 (14, 16-77)
BMI (SD)	26 (5)
Disease characteristics (n=109)	
Knee disorder causing medial tibiofemoral cartilage changes, n*	35
Medial meniscus injury	26
Medial bone marrow edema	6
Medial focal cartilage/osteochrondal damage	9
Medial cartilage degeneration	4
Knee disorder causing lateral tibiofemoral cartilage changes, n*	21
Lateral meniscus injury	17
Lateral bone marrow edema	2
Lateral focal cartilage/osteochrondal damage	5
Lateral cartilage degeneration	4
Duration of complaints (%)	
< 1 month	18 (17)
1 to 6 months	22 (20)
> 6 months	69 (63)
Onset of disease, n (%)	
Traumatic	47 (43)
Clinical symptoms (n=47)	
KOOS questionnaire subscales, score (0-100)(SD)	
Symptoms	63 (18)
Pain	45 (22)
Activities of Daily Living	66 (16)
Sports	74 (20)
Quality of life	35 (20)
T2 relaxation times (n=109)	
Femoral and tibial cartilage, ms (SD)	40 (3)
Weight bearing femoral condyle medial	41 (6)
Posterior femoral condyle medial	38 (4)
Weight bearing tibial plateau medial	40 (5)
Weight bearing femoral condyle lateral	40 (5)
Posterior femoral condyle lateral	37 (5)
Weight bearing tibial plateau lateral	41 (6)

*BMI, Body Mass Index. * Patients can have more than 1 diagnosis*

Table 2. Multivariate linear regression of patient characteristics on total cartilage T2 values

	Age		BMI		Sex	
	β (95% CI)	**p**	**β (95% CI)**	**p**	**β (95% CI)**	**p**
Medial						
Femur weight-bearing	0.34 (0.16; 0.53)	<0.01	-0.02 (-0.20; 0.16)	0.84	0.02 (-0.17; 0.20)	0.9
Femur posterior	0.09 (0.18; 0.54)	<0.01	0.07 (-0.11; 0.25)	0.43	0.01 (-0.17; 0.19)	1.0
Tibia weight-bearing	0.26 (0.07; 0.45)	0.01	0.07 (-0.11; 0.26)	0.44	0.01 (-0.17; 0.20)	0.9
Lateral						
Femur weight-bearing	0.16 (-0.03; 0.35)	0.10	0.14 (-0.05; 0.33)	0.15	-0.41 (-0.23; 0.15)	0.7
Femur posterior	0.00 (-0.20; 0.19)	0.97	0.19 (-0.06; 0.43)	0.13	0.04 (-0.15; 0.23)	0.7
Tibia weight-bearing	0.20 (0.02; 0.38)	0.03	0.25 (0.07; 0.44)	<0.01	0.10 (-0.08; 0.28)	0.3
Total	0.33 (0.16; 0.51)	<0.01	0.20 (0.02; 0.38)	0.03	0.08 (-0.09; 0.26)	0.4

Calculated coefficients are the standardized coefficients (β) with corresponding p value and 95% confidence interval. In this model, the independent variables were responsible for 19% of the variance in T2 relaxation times (R^2=0.19) and no multicollinearity was detected.

Table 3. Subgroups of patients with unicompartimental cartilage damage

Patients with medial cartilage damage	**Medial**		**Lateral**		
n=35	**Mean T2**	**SD**	**Mean T2**	**SD**	**p**
Femur weight-bearing	42	9	39	4	0.05
Femur posterior	37	6	36	4	0.01
Tibia weight-bearing	40	4	40	4	0.5
Patients with lateral cartilage damage	**Medial**		**Lateral**		
n=21	**Mean T2**	**SD**	**Mean T2**	**SD**	**p**
Femur weight-bearing	41	5	39	4	0.2
Femur posterior	37	2	37	4	1.0
Tibia weight-bearing	39	3	42	5	0.02

T2 values in milliseconds. Tested with paired sample t-test. SD: standard deviation

Figures

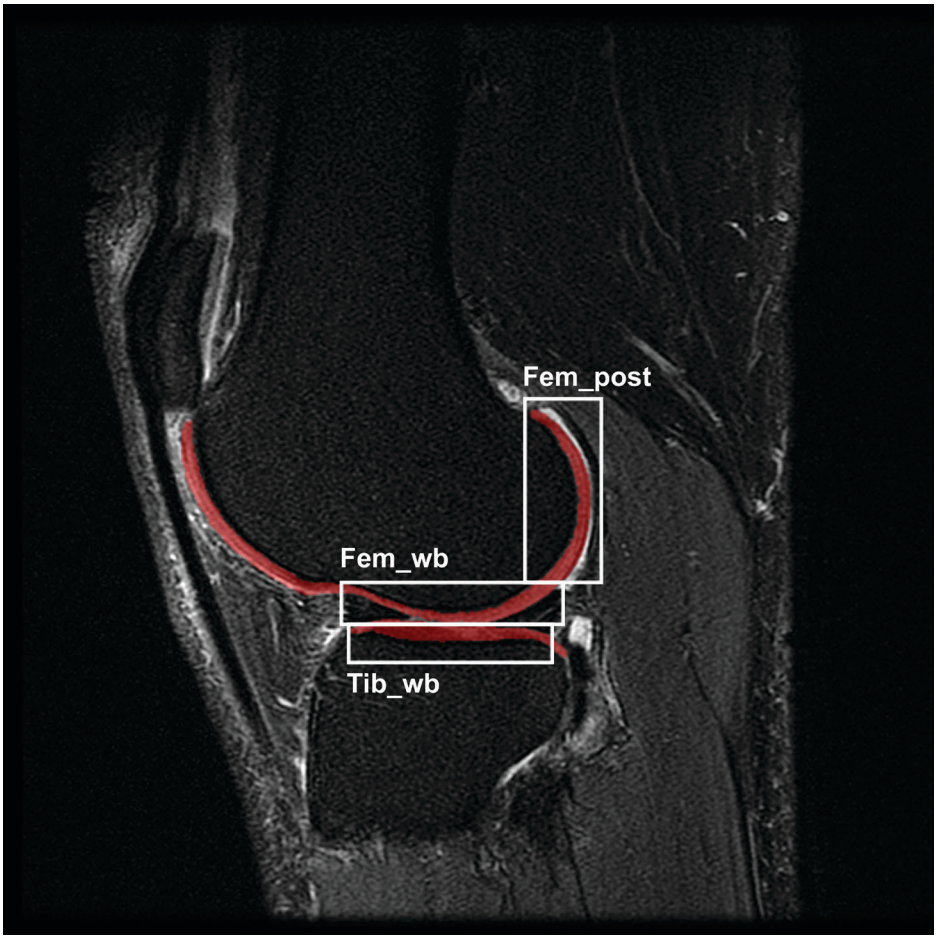


Figure 1. Cartilage segmentation on a T2 weighted image of the lateral compartment. Red area displays the femoral and tibial cartilage; white boxes represent the ROIs. Abbreviations: Fem_wb: weight-bearing femoral condyle; Fem_post: posterior femoral condyle; Tib_wb: weight-bearing tibial plateau.

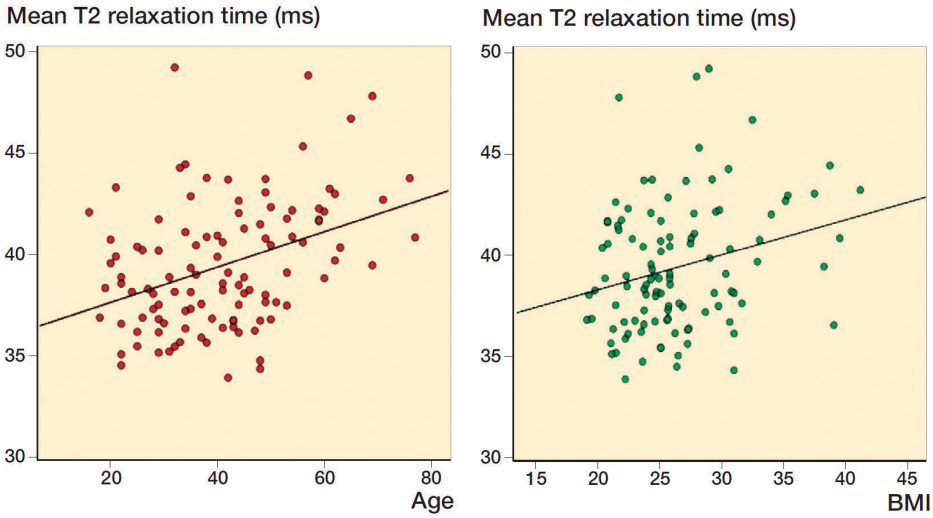


Figure 2. Scatter plots of age and mean T2 (left graph) and BMI and mean T2 (right graph) with corresponding trend lines (age: $R^2 = 0.15$, and BMI: $R^2 = 0.068$). Each circle represents the total tibiofemoral cartilage T2 value of 1 patient.

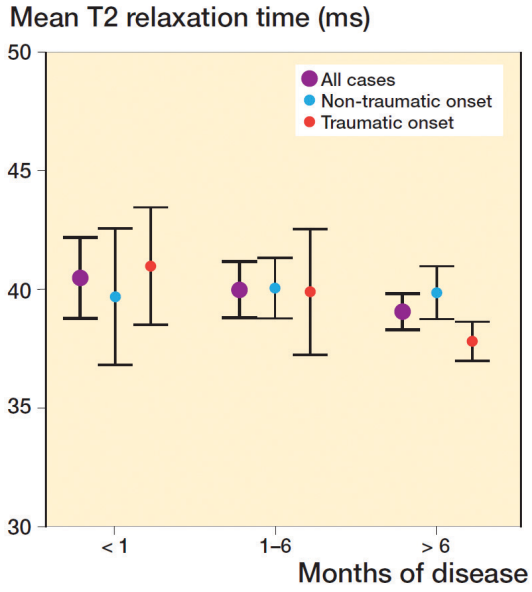
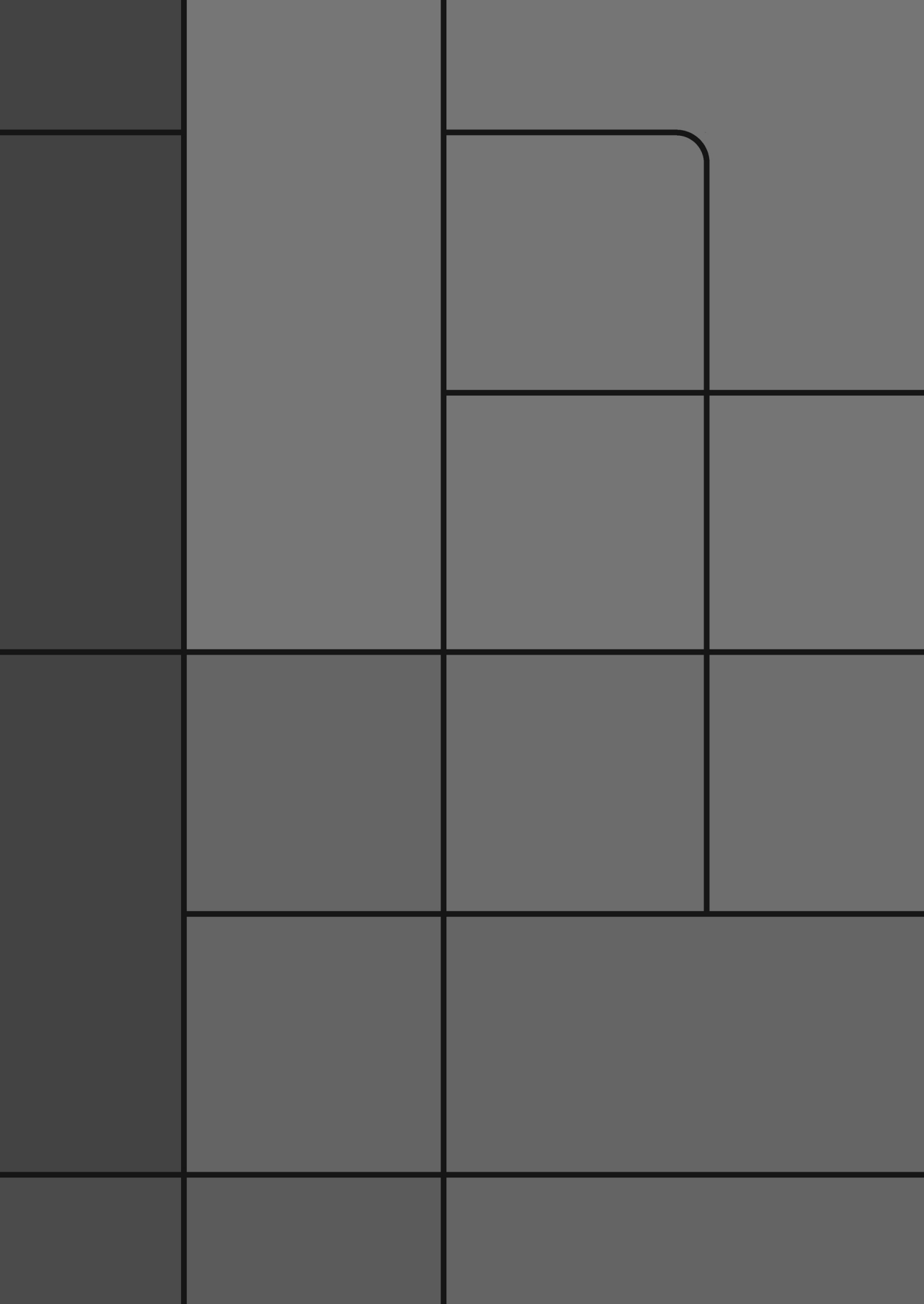


Figure 3. Total tibiofemoral cartilage T2 values with 95% confidence interval for duration of disease for all cases and divided in non-traumatic and traumatic onset groups classified as acute (n = 18 [7 and 11]), subacute (n = 22 [13 and 9]), and chronic (n = 69 [42 and 27]). Effect of duration on total cartilage T2 values for all cases was $\beta = 0.31$ ($p = 0.4$), for non-traumatic onset $\beta = 0.06$ ($p = 0.6$), and for traumatic onset $\beta = -0.30$ ($p = 0.04$) calculated by multiple linear regression analyses with sex, age, and BMI as covariates.



Chapter 5

T2-mapping of healthy knee cartilage: multicenter multivendor reproducibility

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Preliminary results of this study were presented in the thesis of Susanne M. Eijgenraam 'The Meniscus Matters - Novel insights into imaging and treatment of meniscal pathology' (2020)

Abstract

Background

T_2 mapping is increasingly used to quantify cartilage degeneration in knee osteoarthritis (OA), yet reproducibility studies in a multicenter setting are limited. The purpose of this study was to determine the longitudinal reproducibility and multicenter variation of cartilage T_2 mapping, using various MRI equipment and acquisition protocols.

Methods

In this prospective multicenter study, four traveling, healthy human subjects underwent T_2 mapping twice at five different centers with a 6-month-interval. Centers had various MRI scanners, field strengths, and T_2 mapping acquisition protocols. Mean T_2 values were calculated in six cartilage regions of interest (ROIs) as well as an average value per patient. A phantom was scanned once at each center. To evaluate longitudinal reproducibility, intraclass correlation coefficients (ICC), root-mean-square coefficient of variation (RMS-CV), and a Bland-Altman plot were used. To assess the variation of in vivo and phantom T_2 values across centers, ANOVA was performed.

Results

ICCs of the T_2 mapping measurements per ROI and the ROI's combined ranged from 0.73 to 0.91, indicating good to excellent longitudinal reproducibility. RMS-CVs ranged from 1.1% to 1.5% (per ROI) and 0.6% to 1.6% (ROIs combined) across the centers. A Bland-Altman plot did not reveal a systematic error. Evident, but consistent, discrepancies in T_2 values were observed across centers, both in vivo and in the phantom.

Conclusions

The results of this study suggest that T_2 mapping can be used to longitudinal assess cartilage degeneration in multicenter studies. Given the differences in absolute cartilage T_2 values across centers, absolute T_2 values derived from various centers in multicenter multivendor trials should not be pooled.

Introduction

Quantitative magnetic resonance imaging (qMRI) techniques to assess changes in biochemical cartilage composition in osteoarthritis (OA) are emerging.[88] By detecting cartilage degeneration before it is visible on radiography or conventional MRI, qMRI techniques enable early intervention and monitoring of disease progression in OA.[191] T_2 mapping, which provides a marker for collagen integrity without the need for intravenous contrast or specific MRI hardware, is the most widely used qMRI technique in knee OA research.[68, 191-194] Although cartilage T_2 mapping has found wide-spread use in OA research, reproducibility studies on T_2 mapping in a multicenter setting are scarce.[195] Longitudinal reproducibility analyses of multicenter cartilage T_2 mapping have been limited to studies using similar scanners and harmonized MRI acquisition protocols.[194, 196, 197] However, differences in MRI hardware and T_2 mapping sequences, which may be attributable to local requirements and restrictions regarding MRI acquisition, are often present when performing a multicenter trial. Complete standardization of MRI acquisition across different centers is, therefore, not always feasible, especially in large-scale multidisciplinary clinical trials. Little is known about the longitudinal reproducibility of cartilage T_2 values acquired on MRI scanners from different vendors and with non-harmonized acquisition protocols. The aim of the present study was to evaluate the multicenter reproducibility of cartilage T_2 mapping, from a clinical and pragmatic perspective. We assessed the longitudinal T_2 mapping reproducibility and the variation of T_2 relaxation times among various MRI systems with different field strengths and acquisition protocols.

Methods

Study design

Five medical centers located in different geographical parts of The Netherlands participated in this prospective observational study. In these centers, a multicenter randomized controlled trial (RCT) is currently conducted on the outcomes of conservative versus operative treatment of a traumatic meniscal tear (trial number NTR 4511). T_2 mapping is used as an outcome measure for deterioration of knee cartilage two years after a meniscal tear in this study. Four traveling human subjects underwent MR imaging of the knee, including a T_2 mapping sequence, at each of the five centers in one day (i.e., baseline measurements). To evaluate longitudinal reproducibility of T_2 mapping, the exact same experiment was performed six months later (i.e., follow-up measurements). Subjects were scanned in the same order in each center, both at baseline and follow-up. Moreover, centers were visited in the same order and at the same time of day to address potential diurnal variation in T_2 measurements. To assess the variation of T_2 values across centers, cross-validation was performed in the human subjects as well as a phantom. Approval from the Institutional Review Board of our institution (MEC 2014-096) and written consent of all subjects was obtained.

Human subjects and phantom

For in vivo T_2 measurements, the left knee of four healthy volunteers (median age 29 years, range 25-30 years, median BMI 21.5 kg/m^2, three females) was scanned. The subjects had no history of knee pathology and did not report any knee complaints or injuries before or during the 6 months between scans. During baseline- and follow-up measurement days, subjects all had the same physical activity level without significant exercise or heavy loading. The subjects traveled by car; the same car was used during baseline- and follow-up measurements. None of the subjects engaged in significant exercise or heavy loading of the knee two days preceding the measurement days. An in-house developed phantom was scanned once at each center to assess the variation of the T_2 values. The phantom consisted of eight vials of 3 cm diameter, containing various concentrations of manganese chloride (0 to 80 mg/mL). These concentrations were selected to encompass T_2 values within the range of human articular cartilage. [88]

Data acquisition

MRI acquisition parameters are summarized per center in Table 1. MRI scanners manufactured by GE Healthcare (Milwaukee, WI, USA), Siemens (Erlangen, Germany) and Philips (Eindhoven, The Netherlands) were used for this study; three 3-Tesla scanners (GE, Siemens and Philips), and two 1.5-Tesla scanners (both Siemens). Dedicated knee coils were used in each center; either receive only or combined transmit-receive. MRI protocols were optimized in each center according to locally available MRI hardware and software. All knees were scanned in the sagittal plane. For phantom measurements, the same T_2 mapping protocol was used as for human subjects. For the purpose of cartilage segmentation in vivo, a sagittal high-resolution fast-spoiled gradient-echo (FSPGR) sequence with fat-saturation was acquired of each subject at center 1 at baseline. None of the MRI systems or acquisition protocols underwent updates or adjustments during the study period.

Image processing

An in-house developed MATLAB (R2011a; The Math-Works, Natick, MA, USA) extension was used for post-processing analyses of all scans.[167] Rigid registration in 3D provided motion compensation between echo times of the T_2 mappings scans. All T_2 mapping scans were registered to the high-resolution FSPGR scan acquired at baseline at center 1, to ensure that exactly matching regions of interest (ROIs) were measured. Full-thickness cartilage masks of the central portion of the medial and lateral tibiofemoral compartment were manually segmented on the subjects' high-resolution FSPGR scans. Segmentation was performed by a researcher with a medical degree and four years of experience in musculoskeletal imaging (JV) on five slices with a three-millimeter-interval. Subsequently, the segmented masks were divided into six cartilage ROIs, located in the medial and lateral weight-bearing and posterior femoral condyles and tibial plateaus (Figure 1) as scans will be analyzed in the same manner in the aforementioned RCT on the outcomes traumatic meniscal tear treatment. The outer perimeters of the menisci demarcated the weight-bearing ROIs of the femur and tibia. The posterior ROIs contained the femoral cartilage behind the posterior

border of the menisci. Within each ROI, mean T_2 relaxation time was computed using a weighted averaging procedure.[167] Besides T_2 values per ROI, an average T_2 value per patient was calculated to assess the variation of T_2 relaxation times across centers. The automated registration of the follow-up T_2 mapping scan to the high-resolution scan yielded visually inaccurate registration in two measurements (center 3; subject 3 and center 4; subject 4). For these measurements, cartilage was segmented directly on T_2 mapping images while ensuring that the regions matched those segmented on the high-resolution scan. In phantom scans, a central circle of approximately 2 cm diameter was segmented directly on the T_2 mapping images, on four consecutive slices of 3 mm thickness.

Statistical analyses

The longitudinal reproducibility of T_2 measurements in each cartilage ROI and the ROIs combined was evaluated with intraclass correlation coefficients (ICCs) for absolute agreement of single measures, using a two-way random model. As there were not enough subjects to calculate an ICC per center, we pooled the T_2 values of all subjects from all centers. To interpret ICC findings, we used the following scale: poor (ICC < 0.5), moderate (ICC 0.5-0.7), good (ICC 0.7-0.9), or excellent (ICC > 0.9) reproducibility.[198] To assess the reproducibility per center, we calculated coefficients of variation (CVs, defined as the standard deviation (SD) normalized by the mean value of the measurements) of the differences in T_2 measurements between both measurements for each subject. Since averaging the subject's CVs to obtain pooled CVs for each center and for each cartilage ROI is inadequate, we calculated the root-mean-square coefficient of variation (RMS-CV, expressed as a percentage) according to the method of Glüer et al.[199, 200] RMS-CV is defined as the square root of the sum of the squared CVs for each subject, divided by the sample size. An RMS-CV value of zero represents a perfect precision of agreement. A Bland-Altman plot was made per ROI to determine limits of agreement of T_2 measurements, in order to gain insight into the extent and nature of the error (i.e., systematic or random error), and to identify possible outliers. The limits of agreement were defined as the mean difference in T_2 values between baseline and follow-up measurements (i.e., the mean error) ± 1.96 SD.

To assess the variation of T_2 relaxation times across centers, we compared the T_2 relaxation times of the subjects (average T_2 value per subject) of the baseline measurements and the phantom between centers. Variation in T_2 values was analyzed using one-way ANOVA with Dunn's Multiple Comparison Test. Data was tested for normality using Shapiro-Wilk tests. P values < 0.05 were considered statistically significant. Statistical analyses were performed using SPSS version 24.0 (IBM Corp., Armonk, NY, USA, 2016) and GraphPad Prism version 8.0 (GraphPad Software, San Diego California USA, 2018).

Results

Longitudinal reproducibility of in vivo T_2 measurements

The ICCs of the T_2 measurements pooled across all centers ranged from 0.73 to 0.91 for the different ROIs, indicating a good to excellent reproducibility (Table 2). When using the average T_2 values per subject, we found an excellent reproducibility with an ICC of 0.90. In the same table, the RMS-CVs of the longitudinal T_2 measurements per center are presented for the different ROIs and the ROIs combined. The overall (average T_2 value per subject) RMS-CV in each center ranged from 0.6% to 1.6%. The Bland-Altman plot revealed a mean difference of -0.11 milliseconds between baseline and follow-up T_2 measurements (Figure 2). Lowest mean differences were observed in center 1 and center 5, indicating highest reproducibility. A systematic error was not observed.

Two (out of 120) data points of the follow-up measurements were excluded from analysis. The lateral posterior femoral condyle of subject 1 in center 2 and the lateral tibial plateau of subject 4 in center 3 showed T_2 values beyond plausible ranges (> 150 milliseconds). The invalid T_2 value of the first mentioned ROI was due to substantial excess blurring in the slice direction in that particular scan. Non-saturated fat signals, causing partial volume effects, were most likely responsible for the invalid value of the other excluded ROI.

Multicenter variation of in vivo and phantom T_2 measurements

In Figure 3A, the average T_2 values per subject are plotted for each center, showing discrepancies across centers. A statistically significant difference in T_2 values was found between center 1 and center 4 ($p < 0.01$). However, mutual differences in T_2 values between subjects were consistent across all centers. Moreover, phantom T_2 measurements showed a comparable pattern of differences in T_2 values across centers as seen in vivo, especially in vials with lower concentration of manganese chloride (Figure 3B). Phantom stability was verified (ICC 0.90, 95%-CI [0.856–0.928] over a six-month-interval).

Discussion

The reproducibility of qMRI techniques such as T_2 mapping is a highly relevant issue that multicenter studies are facing. In the present study, we evaluated the longitudinal reproducibility and variation of T_2 measurements in different cartilage ROIs in a multicenter setting, using various MRI systems and acquisition protocols. ICCs for longitudinal T_2 measurements ranged from 0.73 to 0.91 with RMS-CVs ranging from 0.6% to 1.6%, indicating good to excellent longitudinal reproducibility. Our results indicate that T_2 mapping allows reliable evaluation of intra-subject changes in cartilage T_2 values, given that subjects are evaluated on the same scanner at each time point. These findings highlight the value of T_2 mapping as non-invasive biomarker to longitudinally assess changes in cartilage tissue composition in clinical trials, and, potentially, in future clinical practice.

Our findings are consistent with a previous single center reproducibility study, using a 3 Tesla scanner, reporting RMS-CVs of 3.2% to 6.3% over a 2-month-interval.[197] A multicenter, single vendor study by Li et al., evaluated longitudinal reproducibility of cartilage T_2 values of two traveling subjects acquired at two locations with similar types of MRI scanner and sequence parameters over a 10-month-interval.[196] In the latter study, a RMS-CV of 5.1% was reported, whereas ICCs were not described. Although using identical scanners and harmonized T_2 mapping protocols would be optimal from an imaging perspective, mandating uniform MRI equipment is not always feasible when performing a multicenter trial. Differences in MRI hardware and T_2 mapping sequences are often present across centers, and local requirements and restrictions (e.g., regarding acquisition time) in participating centers may prevail over optimal imaging strategies. Thus, assessing reproducibility in a multicenter multivendor setting is of key importance for future implementation of T_2 mapping in OA research, such that differences in T_2 values across centers can be taken into consideration. An overall assessment of reproducibility of cartilage T_2 measurements was provided in a multicenter multivendor by Mosher and colleagues.[194] Longitudinal cartilage T_2 measurements were evaluated by pooling 50 subjects, involving patients with OA and asymptomatic control subjects, from five centers using two different MRI vendors. A moderate to excellent reproducibility (ICC between 0.61 and 0.98) was reported over a 2-month-interval, with RMS-CVs ranging from 5% to 9% in healthy volunteers. As none of the subjects in the latter study underwent MRI scanning in more than one scanner, the within-subject reproducibility across centers could not be assessed. To our knowledge, the present work is the first study assessing the longitudinal reproducibility of cartilage T_2 mapping in a multicenter multivendor setting, using traveling human subjects.

When evaluating longitudinal reproducibility of the five participating centers, longitudinal T_2 measurements from center 1 and center 5 showed the lowest RMS-CVs and the lowest mean differences. A potential explanation for this finding could be the use of fast spin echo (FSE) pulse sequences in center 1 and 5 whereas the remaining centers uses spin echo (SE) sequences.[178]

Many factors can potentially cause longitudinal variation in T_2 measurements, apart from biological changes. These include environmental factors (e.g., MRI room temperature), upgrades in MRI hardware or software, changes in phantom composition, subject features (exercise, knee flexion), and diurnal variation in T_2 measurements.[196, 197] In the present study, all efforts were made to maintain conditions constant: stability in room temperatures, and no hardware or software updates during the experiment. Great care was taken to minimize and standardize physical activity level of the subjects, prior to and during scanning days. Furthermore, centers were visited in the same order at baseline and follow-up, and in each center, measurements took place at the same time of day to address potential diurnal variation in T_2 values.

We observed discrepancies in T_2 values across centers, both in vivo and in the phantom. These findings are in line with previous studies on multicenter variation of cartilage T_2 measurements.[197] Several factors could potentially explain the inter-scanner differences in T_2 values we found. First, scanners from three different MRI vendors were used in this study. A multivendor comparability study by Balamoody and colleagues reported significant inter-scanner differences in cartilage T_2 values of 12 healthy subjects across three centers with different MRI vendors (GE Healthcare, Siemens and Philips). As in our study, T_2 values obtained with GE equipment were lower compared to Siemens and Philips T_2 values. A relevant potential source of variation in T_2 values from various MRI vendors are the differences in radiofrequency coil provided by each vendor, in particular the use of receive only versus transmit and receive coils.[201, 202] Dardzinski et al. reported higher cartilage T_2 values and lower RMS-CVs using a receive only coil compared to a transmit and receive coil, similar to our findings.[201] Second, magnetic field strength among centers varied in our study, potentially influencing T_2 values.[203, 204] Finally, different T_2 mapping techniques were used among centers. In center 1, a 3D FSE pulse sequence was used, whereas the remaining centers used 2D sequences. In a study by Matzat et al., the influence of different T_2 mapping sequence protocols in a single scanner was assessed.[178] In the latter study, 2D FSE resulted in 28% (SD 19%) higher T_2 values than 3D FSE. A possible explanation for this could be the stimulated echo effect in the second echo time and onwards. This might have led to artificially higher T_2 values in center 2, 3, 4 and 5, compared to the 3D sequence of center 1. Also, the application of fat saturation in T_2 mapping sequences could have been a potential source of variation in T_2 values across centers. Center 2 and center 3 used a non-fat-suppressed sequence and generated relatively low T_2 values. This is in line with a study by Ryu et al., reporting that non-fat-suppressed T_2 mapping results in higher T_2 values and less reproducible T_2 measurements compared to fat-suppressed T_2 mapping.[205] A systematic study investigating the causes of the observed differences in T_2 values across centers, with the aim of providing protocols that result in comparable T_2 values for different vendors and T_2 mapping techniques would be valuable, but this is beyond the scope of the current study. For now, we conclude that absolute T_2 values across centers should not be assumed to be comparable and should therefore not be pooled. In multicenter clinical trials, researchers should focus on intra-subject T_2 changes rather than absolute mean T_2 values across subject groups.

The present study has limitations that must be noted. First, our sample size was small. We opted to perform T_2 measurements at each of the five centers in one day, hence only a limited sample size was feasible. Consequently, this study was statistically underpowered to report ICCs for longitudinal reproducibility of each center individually. With a larger sample size it might have been possible to find reference T2 values of healthy cartilage for each scanner (brand and field strength), which was beyond the scope of the current study. Second, as our study was limited to healthy subjects, it is not sure whether these findings are generalizable to OA subjects and care should be taken to use this information in other contexts such as cartilage repair.

Conclusions

In this multicenter multivendor study, in vivo cartilage T_2 mapping showed a good to excellent longitudinal reproducibility. Our results suggest that T_2 mapping can be used to longitudinally assess intra-subject changes in cartilage degeneration in multicenter studies, yet these findings must be interpreted with caution considering the size and nature (i.e., healthy subjects) of the study population. Given the variation in T_2 values across centers, absolute T_2 values obtained in various centers in multicenter multivendor clinical trials should not be pooled.

Tables

Table 1. MRI sequence parameters

	Center 1	Center 2	Center 3	Center 4	Center 5
Scanner	3-T Discovery MR750, GE Healthcare, Milwaukee, WI, United States	1.5-T Aera, Siemens, Erlangen, Germany	1.5-TAera, Siemens, Erlangen, Germany	3-T Skyra, Siemens, Erlangen, Germany	3-T Achieva dStream, Philips Healthcare, Best, The Netherlands
Sequence type	3D Fast Spin Echo FS	2D Spin Echo non-FS	2D Spin Echo non-FS	2D Spin Echo FS	2D Fast Spin Echo FS
Matrix (RO x PE)	288 x 192	192 x 144	256 x 256	256 x 190	300 x 247
Slice thickness/ spacing	3/0	3/0.2	3/0.3	3/0.4	3/0.3
Number of slices	36	28	30	27	40
Number of echoes	5	8	6	8	9
TE (ms)	3; 13; 27; 41; 68	8; 16; 24; 32; 40; 48; 56; 64	14; 28; 41; 55; 69; 83	9; 17; 26; 34; 43; 51; 60; 68	7; 15; 23; 29,37; 44; 51; 58; 66
TR (ms)	1263	2000	2690	2170	3582
FOV (cm)	15	18	16	18	15
Coil	8-channel S&R rigid	15-channel S&R rigid	15-channel S&R rigid	15-channel S&R rigid	8-channel knee R rigid
Scan Time (mm:ss)	09:41	3.06	07:15	06:27	08:31

Abbreviations: RO = readout, PE = phase encoding, TE = echo time, TR = repetition time, FOV = field of view, FS = fat suppression, S&R = send and receive, R = Receive

Table 2. Agreement of longitudinal in vivo T2 measurements per cartilage ROI

	ICC		RMS-CV				
	ICC	**CI-95**	**Center 1**	**Center 2**	**Center 3**	**Center 4**	**Center 5**
Femoral cartilage							
Weight-bearing							
Medial	0.91	0.78 - 0.96	1.6	3.4	5.2	1.2	0.9
Lateral	0.82	0.59 - 0.92	3.3	2.2	3.3	4.2	1.3
Posterior							
Medial	0.91	0.80 - 0.97	1.5	4.0	2.3	1.2	2.0
Lateral	0.85	0.66 - 0.94	1.1	6.2	2.4	2.9	1.1
Tibial cartilage							
Medial	0.86	0.69 - 0.94	2.7	1.8	4.0	4.5	1.4
Lateral	0.73	0.44 - 0.89	2.8	1.2	2.7	6.2	1.1
Overall (ROIs combined)	0.90	0.86 – 0.93	1.1	1.3	1.4	1.6	0.6

Data of the human subjects was pooled. For the ICC, data of all centers was pooled. RMS-CV shows the precision of agreement for longitudinal T2 measurements in human subjects, shown as percentage. The lower the RMS-CV, the higher the precision. ROI = region of interest, ICC = Intraclass Correlation Coefficient, CI-95 = 95% confidence interval, RMS-CV = root mean square coefficient of variation

Figures

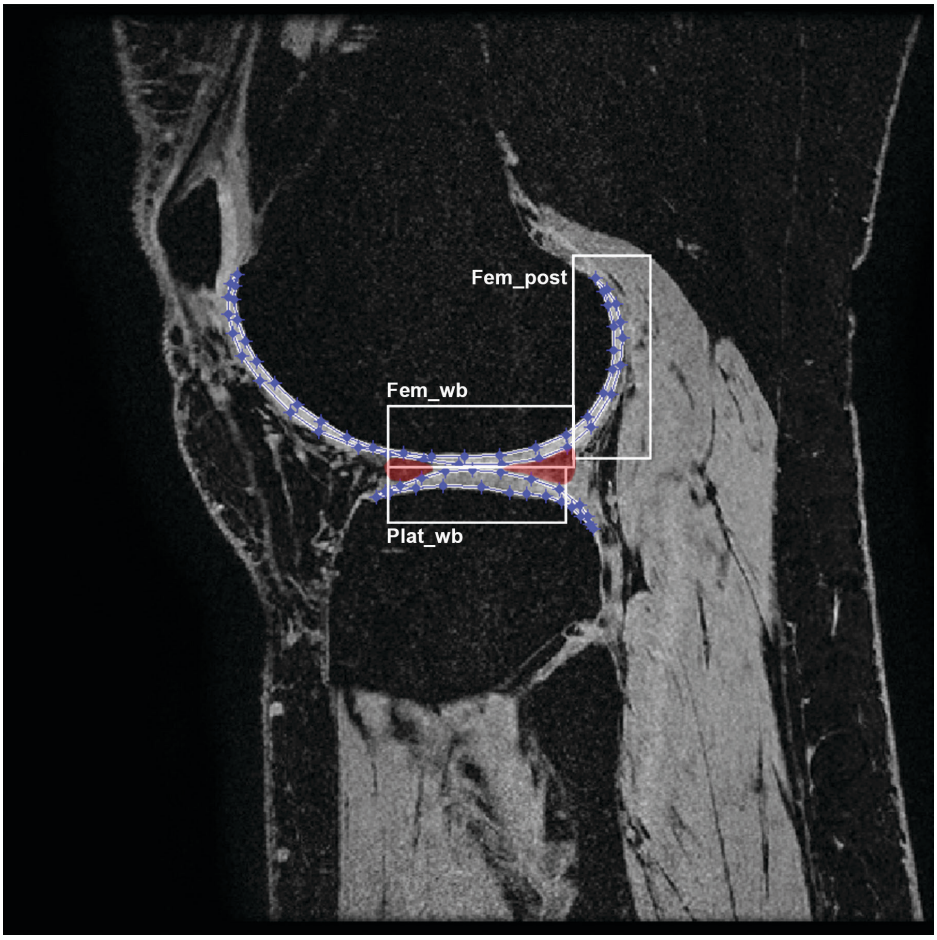


Figure 1. Cartilage segmentation on sagittal high-resolution FSPGR image, lateral compartment. Blue dotted lines surround the segmented mask; white boxes represent the ROIs. Fem_post: posterior femoral condyle; Fem_wb: weight-bearing femoral condyle; Plat_wb: weight-bearing tibial plateau.

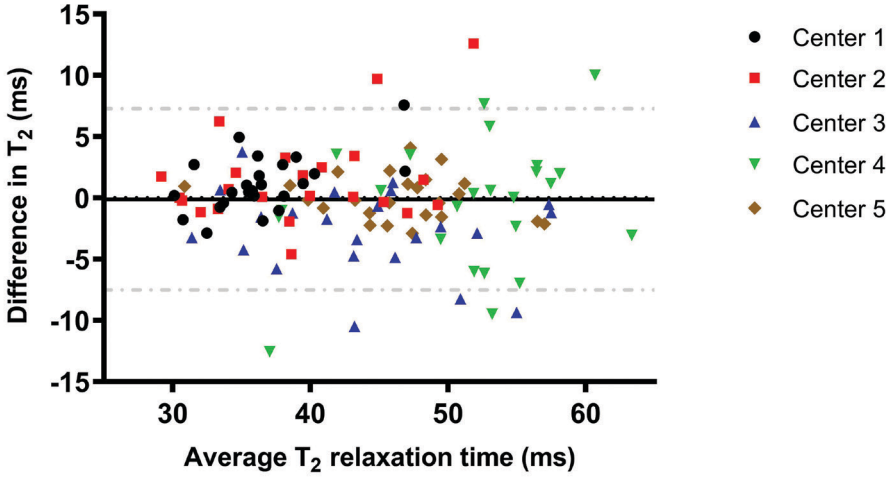


Figure 2. Bland-Altman plot showing the differences in *in vivo* T_2 values between baseline and follow-up against the mean T_2 values plotted per cartilage ROI for each subject. Each colored shape represents the four subjects with each six ROIs. The bold line represents the mean difference, dotted lines represent the limits of agreement.

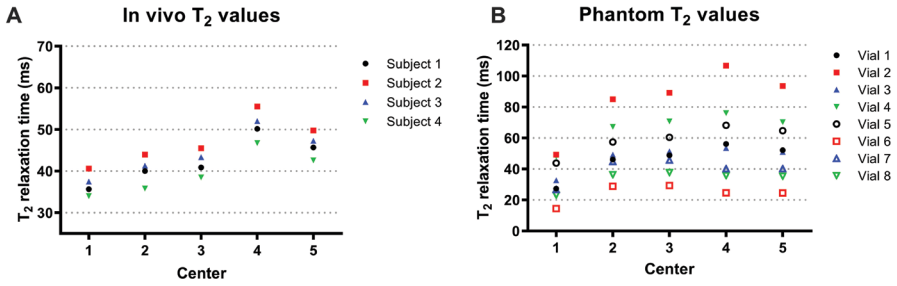
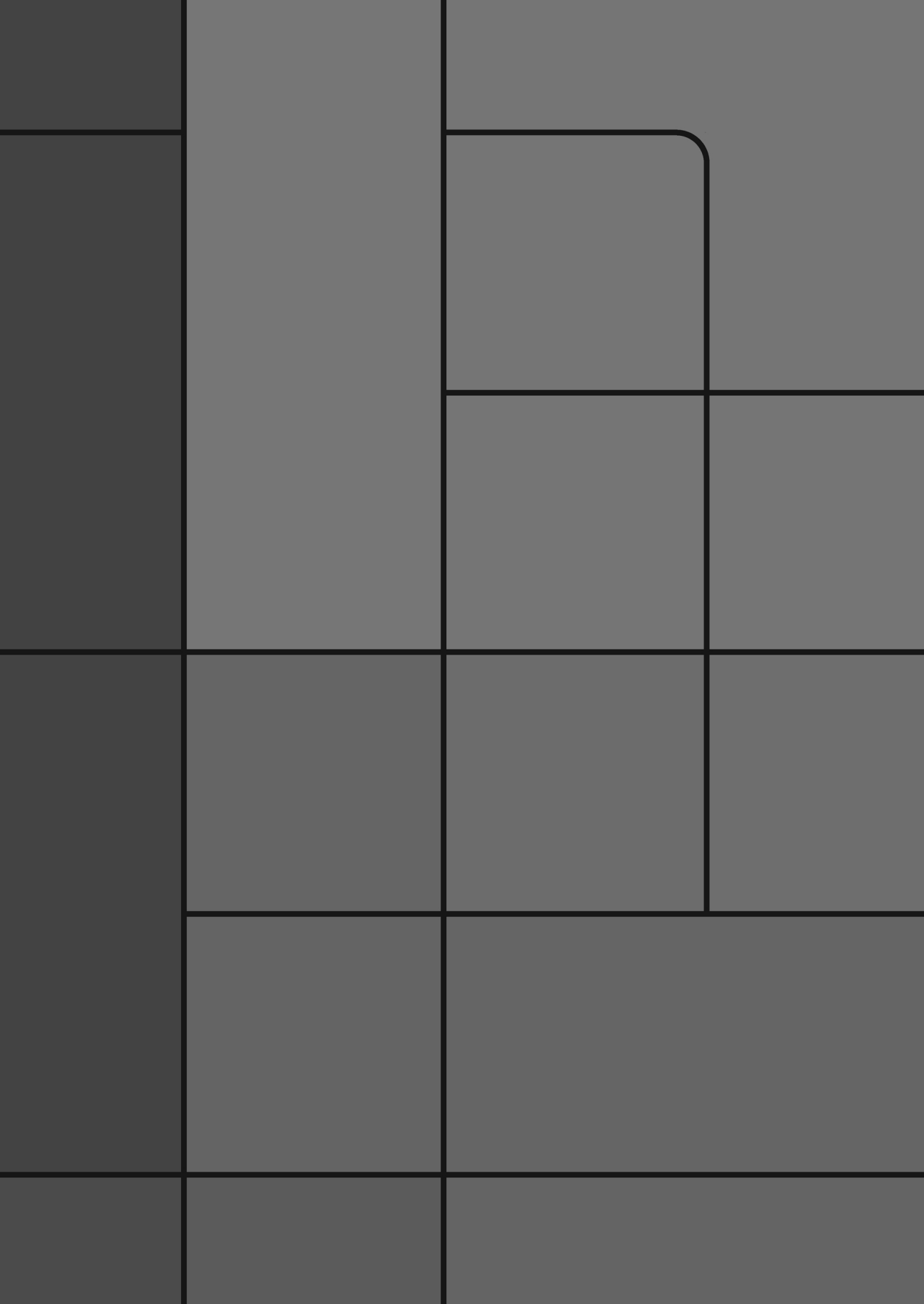


Figure 3. Average T_2 values of subjects and phantom vials per center. (A) Baseline average T_2 values per subject in each center; (B) Phantom T_2 values plotted per vial in each center. The concentration of manganese chloride for each vial was: vial 1 =0%, vial 2 =5%, vial 3 =10%, vial 4 =15%, vial 5 =20%, vial 6 =30%, vial 7 =50%, and vial 8 =80%.



Chapter 6

Possibility of Quantitative T2-Mapping MRI of Cartilage Near Metal in High Tibial Osteotomy: A Human Cadaver Study

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Abstract

T2-mapping is a widely used quantitative MRI technique in osteoarthritis research. An important challenge for its application in the context of high tibial osteotomy (HTO) is the presence of metallic fixation devices. In this study, we evaluated the possibility of performing T2-mapping after a HTO, by assessing the extent of magnetic susceptibility artifacts and the influence on T2 relaxation times caused by two commonly used fixation devices. T2-mapping with a 3D fast spin-echo sequence at three Tesla was performed on 11 human cadaveric knee joints before and after implantation of a titanium plate and screws (n = 5) or cobalt chrome staples (n = 6). Mean T2 relaxation times were calculated in six cartilage regions, located in the distal and posterior cartilage of femoral condyles and the cartilage of tibial plateaus, both medially and laterally. T2 relaxation times before and after the implantation were compared with paired t-tests and Wilcoxon rank tests. Due to the extent of the magnetic susceptibility artifact, it was not possible to segment the knee cartilage and thus calculate T2 relaxation times in the lateral weight-bearing femoral and tibial cartilage regions only in the cobalt chrome group. In all cartilage regions of the titanium implanted knees and those unaffected by artifacts due to cobalt chrome implants, T2 relaxation times did not significantly differ between the two scans. Our results suggest that accurate T2-mapping after a HTO procedure is possible in all areas after implantation of a titanium fixation device and in most areas after implantation of a cobalt chrome fixation device.

Introduction

Osteoarthritis (OA) causes a tremendous burden for patients and society. The knee is one of the most affected joints, with a prevalence of radiographically confirmed knee OA of 37.4% in patients over 60 years of age in the United States.[206] The medial tibiofemoral compartment is most commonly affected, especially when a varus malalignment is present.[24, 25] For younger and physically active patients with medial knee OA and a varus knee malalignment, a high tibial osteotomy is a successful therapeutic option to prevent or postpone arthroplasty.[108, 135] In HTO, the alignment of the leg is transferred from varus to valgus, thereby reducing the load on the medial knee compartment. This shift in load distribution can be achieved by creating a wedge at the medial side of the proximal tibia: The medial open wedge HTO (owHTO). Alternatively, a bony wedge can be surgically removed from the lateral side of the proximal tibia: The lateral closed wedge HTO (cwHTO). In both techniques, the osteotomy is most commonly fixated using a titanium (locking) plate and screws. For the cwHTO it is also possible to fixate the osteotomy using cobalt chrome staples.

Quantitative MR imaging is increasingly applied to evaluate the success of joint preserving OA therapies, of which HTO is an example.[207] Compared to conventional radiography and MRI that only visualize relatively advanced signs of degeneration, quantitative MR imaging has the advantage of assessing biochemical composition of cartilage determining cartilage components and possibly detecting cartilage deterioration at an early stage of the OA process.[88]

A well-validated and widely used quantitative MR imaging technique for articular cartilage is T2-mapping which measures collagen content and network integrity, expressed as T2 relaxation times.[160, 208] An important challenge for the application of quantitative MRI techniques in the context of HTO is the presence of metal implants after the procedure. This metal will cause magnetic susceptibility artifacts that may influence the quantitative MRI outcomes. To date, application of quantitative cartilage MRI in the proximity of metal implants has been sparsely reported. Delayed Gadolinium enhanced MRI of cartilage (dGEMRIC) was performed after the HTO in a few studies.[105, 107, 209] However, reports on the possible influence of the metal on the quantitative MR results are lacking. Furthermore, as the extent of metal artifacts depends heavily on the MR acquisition technique, results pertaining to dGEMRIC cannot be generalized to other quantitative imaging techniques such as T2-mapping.

In this study, we assessed the possibility of quantitative T2-mapping in the proximity of titanium plate and screws used in owHTO and cobalt chrome staples for cwHTO in fresh-frozen human cadaveric knees. We hypothesized that magnetic susceptibility artifacts could render segmentation of the cartilage in certain regions of the knee impossible. We also hypothesized that these artifacts might have an influence on the T2 relaxation times even when artifacts or geometric distortion are not observed visually.

Methods

Study Subjects

In the period between May 2014 and November 2015, 12 fresh-frozen human cadaveric knee joints were acquired from the donation program of Department of Anatomy of our institution. In The Netherlands, people who donated their body via an academic donation program have specifically expressed their wish in writing to donate their body to science and education. Age and gender were not available for most of the specimens. The size of the specimens had to be at least mid-diaphyseal femur to mid-diaphyseal tibia. Another requirement was that the joint capsule was intact so as to prevent artifacts caused by air in the joint. One knee had to be excluded because the first MRI indicated an insufficient amount of articular cartilage to perform adequate T2 measurements. The knee joints were scanned before and after the implantation of a titanium or cobalt chrome fixation device. Five (two right knees) knees received the titanium implantation material and six knees (two right knees) the cobalt chrome implantation material. Before handling the specimens, they were defrosted to room temperature.

Operation Technique

After the first MRI sessions, the fixation part of the HTO procedure was simulated by inserting fixation material into the specimen by an experienced orthopedic surgeon according to the appropriate surgical techniques. In anatomic specimens that received the titanium implantation material (TomoFix, DePuy Synthes, PA, USA), the tibia was approached from the medial side. The titanium plate was placed alongside the proximal tibia and fixated with eight titanium locking screws (Figure 1). The three most proximal screws were placed parallel to the tibial cartilage, approximately 1 cm below it. For the cobalt chrome implantation material (Stepped High Tibial Osteotomy Staples, Stryker, MI, USA), the proximal knee was approached from the lateral side. The staples were also positioned approximately 1 cm below the tibial cartilage (Figure 2). Correct insertion of the fixation material was confirmed with fluoroscopy. The actual osteotomy was not performed since this would not influence the outcomes of the study and would only incur the risk of air-induced artifacts.

MRI Acquisition

All subjects were scanned before and after the implantation of the titanium and cobalt chrome fixation material on a 3T MR system (Discovery MR750; GE Healthcare, Milwaukee, WI, USA) with a dedicated eight-channel transmit and receive knee coil (Invivo, Gainesville, FL, USA). A 3D fast spin echo sequence was used for T2-mapping with 5 echo times (3, 13, 27, 40, 68 ms); 3 mm slice thickness; and an in-plane resolution of 0.5x0.8 mm.[166] The scan time was approximately 9:40 minutes (Table 1).

Image Processing

Before quantitative analysis, the T2-mapping scans were visually inspected for the extent of the artifacts. If the artifact caused distortion of the cartilage, this region was omitted

for segmentation. For the quantitative post-processing of the MR images, an in-house developed Matlab (R2011a; The Math-Works, Natick, MA, USA) extension was used. Full-thickness cartilage masks were manually segmented on seven slices with a 3 mm interval on the T2-mapping sequence by a researcher with a medical degree and 3 years of experience in musculoskeletal research. After segmenting the cartilage, six cartilage regions of interest (ROI) were defined. These regions were located in the weight-bearing and posterior femoral condyles and in the tibial plateaus, both in the medial and lateral compartment of the knee. We defined "weight-bearing" as the cartilage section within the outer perimeters of the menisci. The posterior ROIs contained the femoral cartilage area behind the posterior horn of the menisci. Mean T2 was calculated using a weighted averaging procedure within each ROI. Automated rigid registration in 3D was used for motion compensation between echo times within one T2-mapping sequence.[167]

Statistical Analyses

Normal distribution of the data was tested using the Shapiro-Wilk method. The scans before and after the implantation of the fixation material were tested for statistically significant differences using paired t-tests for the regions that showed normal distribution. In regions that did not show normal distribution, a Wilcoxon-Rank test was used to test the influence of the implantation material on the T2 relaxation times. A p-value smaller than 0.05 was considered statistically significant. The analyses were performed using SPSS 21.0 (IBM Corp, Armonk, NY, USA).

Results

Titanium Plate and Screws

Extent of Metal-Induced Artifacts

On the fast spin echo T2-mapping images, moderate magnetic susceptibility artifacts were observed around the titanium material (Figure 3). The artifacts in proximity of the most proximal screws, located parallel to the tibial plateau, did not extend into the cartilage. Besides the artifact, cancelation of the fat suppression was seen in a larger area. Delineation of cartilage borders was still possible due to the limited extent of the artifact.

T2 Relaxation Times

The average time interval between scans was 2 hours and 13 minutes (range 1 hour 53 minutes – 2 hours 34 minutes). The mean change in T2 relaxation times of the six ROIs before and after the implantation of the titanium plate and screws ranged from -4.4 to 2.0 ms (Table 2). Representative T2 maps are displayed in Figure 3. T2 relaxation times were normally distributed in all regions except for those in the lateral weight-bearing tibial plateau on the MRI scan acquired before implantation of the titanium material. No statistically significant differences were found in any of the ROIs between the two scans.

Cobalt Chrome Staples

Extent of metal-induced artifacts

The cobalt chrome staples caused artifacts that were much larger than those of the titanium material (Figure 4). They caused distortion of the lateral tibial cartilage in all patients. In two patients, the contour of the lateral weight-bearing femoral cartilage was also distorted. In the other patients, signal loss of the lateral weight-bearing femoral cartilage was seen. Although the implanted material was only situated in the lateral compartment of the tibia, signal loss was also seen in some slices on the medial side. These artifacts, however, were all observed at least 1 cm below the cartilage.

T2 Relaxation Times

The average time interval between scans was 2 hours and 33 minutes (range 2 hour 2 minutes – 3 hours 18 minutes). Because of the distortion of the lateral weight-bearing tibial and femoral cartilage, it was not possible to segment cartilage masks and calculate T2 relaxation times in these regions. Representative T2 maps are displayed in Figure 4. The mean change in T2 relaxation times of the measurable ROIs before and after the implantation of the cobalt chrome staples ranged from -2.9 to -0.1 ms (Table 3). All data showed a normal distribution. No statistically significant differences were found.

Discussion

In our study, we investigated the extent and influence of magnetic susceptibility artifacts caused by titanium and cobalt chrome fixation devices used in HTO procedures for medial knee OA. We found moderate artifacts caused by titanium material which allowed accurate T2 relaxation time measurements in all regions. The artifacts caused by the cobalt chrome staples precluded T2 relaxation time measurements in the lateral weight-bearing femoral and tibial ROI.

We found no statistically significant difference in cartilage T2 relaxation times between the scans made before and after implantation of the titanium fixation material. However, we observed a trend towards decreased T2 relaxation times in the lateral weight-bearing tibial plateau after implantation. Somewhat counterintuitively, this observation could not be explained by the position of the screws. The decreased T2 relaxation times were attributable to three subjects in which the screws were placed parallel to and at least 1 cm underneath the tibial articular surface. Conversely, in one patient in which one of the screws was positioned suboptimally, that is, imparallel to the tibial plateau, and reached almost as far as the subchondral bone plate in the lateral compartment, there was hardly a difference in T2 relaxation times between the two scans (0.1 ms). The cause of this large, albeit not statistically significant, decrease in T2 relaxation times in this region needs

further investigation. Nevertheless, we believe that our findings indicate that it is possible to perform T2-mapping in the proximity of a titanium HTO fixation device.

To our knowledge, no previous study has been published on T2 relaxation times of knee articular cartilage near a titanium HTO implant. Previous studies analyzed cartilage near titanium implantation material with other quantitative MRI techniques, or studied other joints than the knee. Authors who studied dGEMRIC near titanium HTO implants in a clinical setting reported contradictory results on its feasibility. For example, Rutgers et al. encountered enormous metal-induced artifacts that required hardware removal before performing a reliable dGEMRIC scan.[105] In contrast, Parker et al. performed dGEMRIC multiple times after HTO titanium hardware implantation without reporting difficulties, but without describing the extent of the artifacts.[107] Experiments in vivo and in phantoms by d'Entremont et al. showed that a saturation recovery pulse sequence resulted in better performance than an inversion recovery pulse sequence when performing dGEMRIC in the presence of titanium and stainless steel hardware.[209, 210] Studies using T2-mapping of cartilage after a surgical procedure using titanium screws in the ankle did not report the extent of the artifacts or the possible influence of the hardware on T2 relaxation times.[211, 212]

The cobalt chrome staples caused more extensive artifacts in the T2-mapping scans of the human cadaver knee cartilage compared to the titanium material. These artifacts caused distortion of the lateral tibial and femoral weight-bearing cartilage ROIs and made it impossible to segment the cartilage in these regions for the calculation of T2 relaxation times. However, the T2 relaxation times of the medial cartilage ROIs and the lateral posterior cartilage ROI did not statistically significantly differ between the scans acquired before and after implantation of the cobalt chrome staples. As a result, T2-mapping could still play an important role as a quantitative outcome measure in studies investigating the effect of the HTO procedure using MRI. We are not aware of other studies that used T2-mapping in the proximity of cobalt chrome HTO implantation material, but the observation that cobalt chrome causes larger MR artifacts than titanium has been well reported. In fact, major artifacts encountered on MR imaging after hip joint prostheses, which are generally made of cobalt chrome, have led to the development of metal artifact reducing MRI sequences.[213-215] At present, application of these novel imaging techniques in conjunction with quantitative relaxometry is limited by lengthy acquisition times.

In this study, we investigated titanium and cobalt chrome materials commonly used for HTO procedures. While titanium is the most frequently used material in HTO, other fixation devices are available. For the medial open wedge HTO technique, polyetheretherketone and stainless steel plates with titanium or stainless steel screws are on the market. A closed wedge osteotomy can also be fixated with a titanium plate and screws in a similar manner to the open wedge technique. Although our results cannot be generalized to other types of implantation material, we assume that reliable T2 relaxation times of knee cartilage can be obtained when artifacts do not cause visual distortion of the MR images. Titanium material

should be positioned at least 1 cm below the cartilage surface. In case of materials that are more ferromagnetic, such as iron or cobalt chrome, it seems impossible to perform T2-mapping in the compartment in which the material is placed due to extensive artifacts.

One of the strengths of our study is that we were able to mimic the actual HTO procedure with accurate geometric positioning of the implant material. Furthermore, using knees of anatomical specimen enabled us to scan the knee immediately before and after implantation of the fixation material, which would be impossible in living patients. In this way, we minimized the influence of variables other than the material on the T2 relaxation time measurements. Another strength is the use of a fast spin echo (FSE) pulse sequence for T2-mapping, which is known to be less susceptible to metal artifacts.

A limitation of our study is that we cannot exclude a possible effect of the metallic implants on the T2 relaxation times based on the 95% confidence interval due to insufficient power. For a validation study based on equivalence, we would need at least 79 subjects to exclude a difference, depending on the population and region. Including this amount of subjects for our research question would not have been feasible. Second, our study used cadaveric knees in which actual T2 values may be different to those of patients. In absence of normal physiology, the anatomical specimen were scanned at room temperature. Although the T2 relaxation time dependency on temperature is relatively small, the T2 relaxation times observed in this study were generally higher than reported for healthy and osteoarthritic cartilage.[216] The absolute values of T2 relaxation time, however, were considered of less importance as we were primarily interested in possible differences between the scans. Furthermore, there is no evidence to suggest that the influence of the titanium and cobalt chrome materials on the cartilage T2 relaxation times ex vivo would be different in vivo.

In conclusion, our results show that T2-mapping is possible in all regions after implantation of a titanium plate and screws. When cobalt chrome staples are used for a cwHTO procedure, T2-mapping is possible in most ROIs except for the lateral weight-bearing femoral and tibial ROI due to distortion of the cartilage by magnetic susceptibility artifacts. Our study suggests that when metal artifacts do not visually distort the MR images, obtaining reliable T2 relaxation times of knee articular cartilage is possible after an HTO procedure. We recommend using titanium fixation materials over cobalt chrome when quantitative measurements like T2-mapping are used in clinical trials on HTO.

Tables

Table 1. MR imaging parameters

Scanner	3T Discovery MR750 (General Electric Healthcare, Milwaukee, WI, USA)
Coil	8-channel dedicated phased array knee coil (Invivo, Gainesville, FL, US)
	T2 mapping
Plane	Sagittal
Imaging mode	3D
Sequence	FSE
Frequency	288
Phase	192
N° of slices	36
Slice thickness (mm)	3
Spacing (mm)	0
Field of View (mm)	150
Flip angle (degrees)	90
In-plan resolution (mm)	0.5 x 0.8
Echo time (ms)	3, 13, 27, 40, 68
Repetition time (ms)	1263
Bandwidth (Hz/pixel)	244
Fat saturation	Yes
Scanning time (min)	9.40

FSE: fast spin echo; FSPGR: fast spoiled gradient-echo; ms: milliseconds; mm: millimeter; Hz: Hertz; min: minutes

Table 2. Mean T2 relaxation times and T2 change before and after implantation of titanium material

	Without plate and screws			With plate and screws			Change			
	Mean (ms)	95% CI (ms)		Mean (ms)	95% CI (ms)		Mean (ms)	95% CI (ms)		p-value
Weight-bearing femoral condyle										
Lateral	56.7	50.3	63.2	57.8	54.5	61.2	1.1	-2.4	4.5	0.440
Medial	57.3	54.3	60.3	58.2	55.7	60.7	0.7	-1.0	2.4	0.140
Posterior femoral condyle										
Lateral	48.8	45.4	52.2	50.8	45.6	55.9	2.0	-0.5	4.4	0.092
Medial	57.4	53.3	61.4	58.1	52.7	63.4	0.7	-4.7	6.2	0.740
Weight-bearing tibial plateau										
Lateral	62.0*	58.4	65.6	57.6	53.5	61.7	-4.4	-8.2	-0.7	0.063**
Medial	55.2	50.9	59.6	55.0	49.5	60.6	-0.2	-2.4	2.1	0.826

ms = milliseconds; 95% CI = 95% confidence interval. Statistical significance was tested using paired t-tests. Value marked with an * did not show normal distribution and was tested using a Wilcoxon-Signed-Ranks test (**). As means and medians were very similar, we choose to also present means and 95% CI for abnormal distributed data.

Table 3. Mean T2 relaxation times and T2 change before and after implantation of cobalt chrome staples

	Without staple			With staple			Change			
	Mean (ms)	95% CI (ms)		Mean (ms)	95% CI (ms)		Mean (ms)	95% CI (ms)		p-value
Weight-bearing femoral condyle										
Medial	62.0	49.6	74.5	61.0	52.8	69.2	-1.1	-6.0	3.9	0.612
Posterior femoral condyle										
Lateral	56.3	47.9	64.7	53.4	49.0	57.8	-2.9	-9.0	3.2	0.275
Medial	56.7	51.1	62.4	54.7	50.1	59.2	-2.1	-6.2	2.1	0.260
Weight-bearing tibial plateau										
Medial	56.9	50.0	63.7	56.8	49.4	64.1	-0.1	-1.4	1.2	0.869

ms = milliseconds; 95% CI = 95% confidence interval. Statistical significance was tested using paired t-tests. Due to artifacts, T2 relaxation time measurements were not possible in the lateral weight-bearing femoral and tibial ROI.

Figures

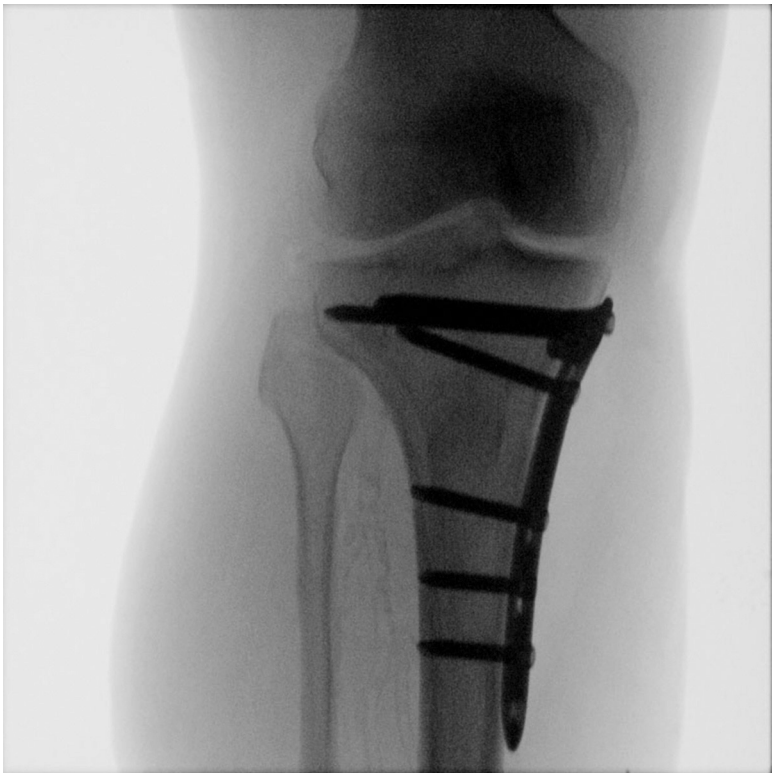


Figure 1. X-ray after implantation of titanium plate and screws. Image made before inserting the most distal screw.

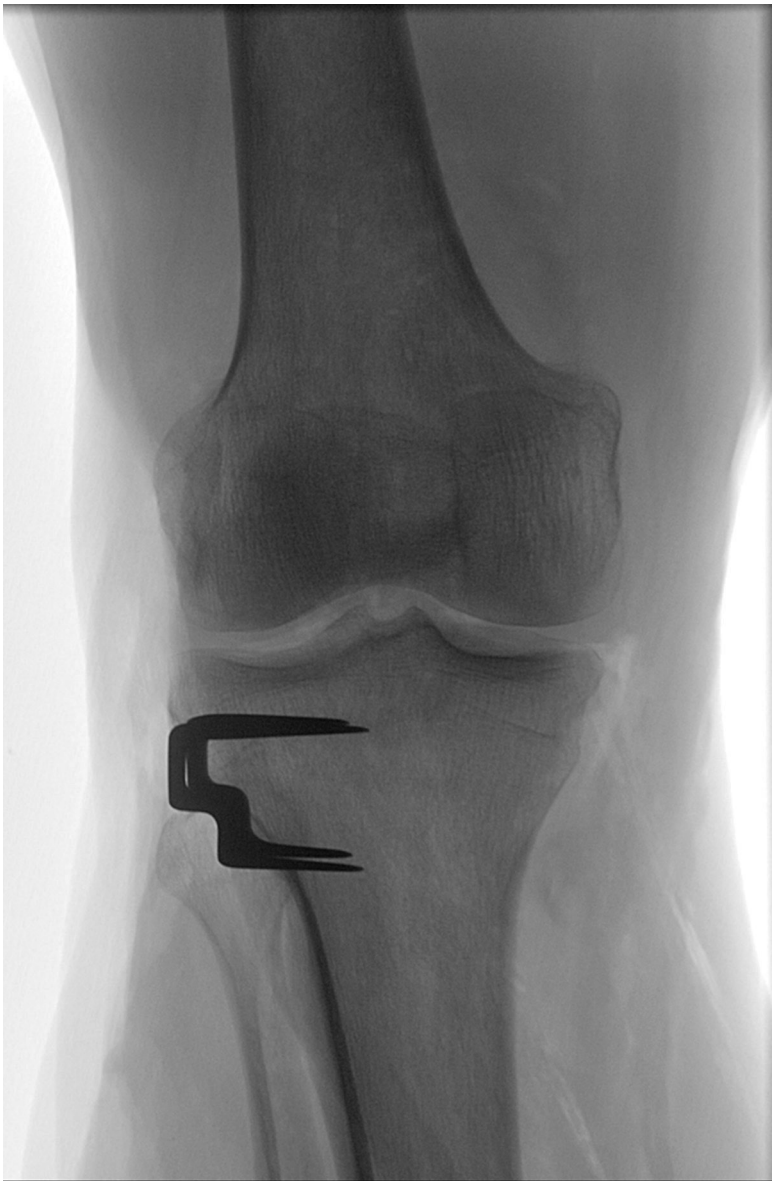


Figure 2. X-ray after implantation of two cobalt chrome staples.

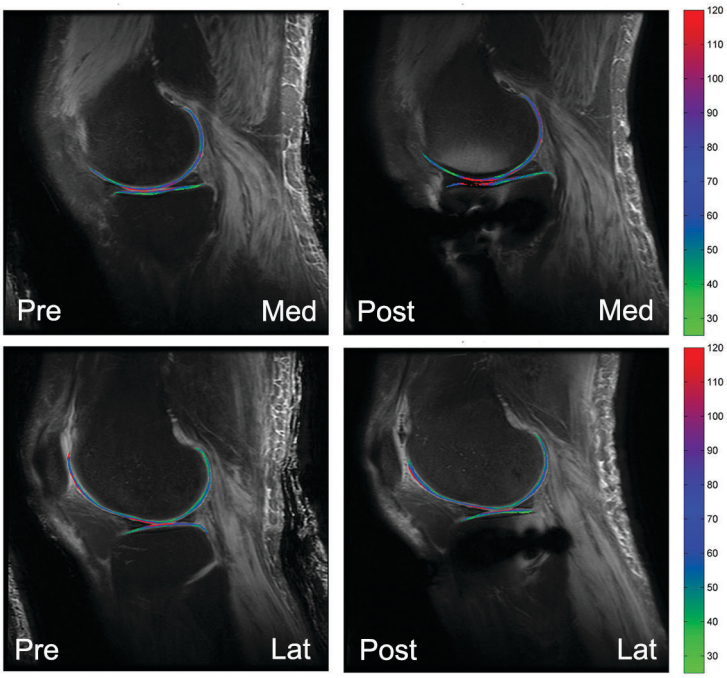


Figure 3. Cartilage T2 color maps with and without the titanium plate and screws on the T2 mapping sequence. Moderate magnetic susceptibility artifacts caused by the material are seen on the right-hand images Pre, before implantation; Post, after implantation; Med, Medial compartment; Lat, Lateral compartment.

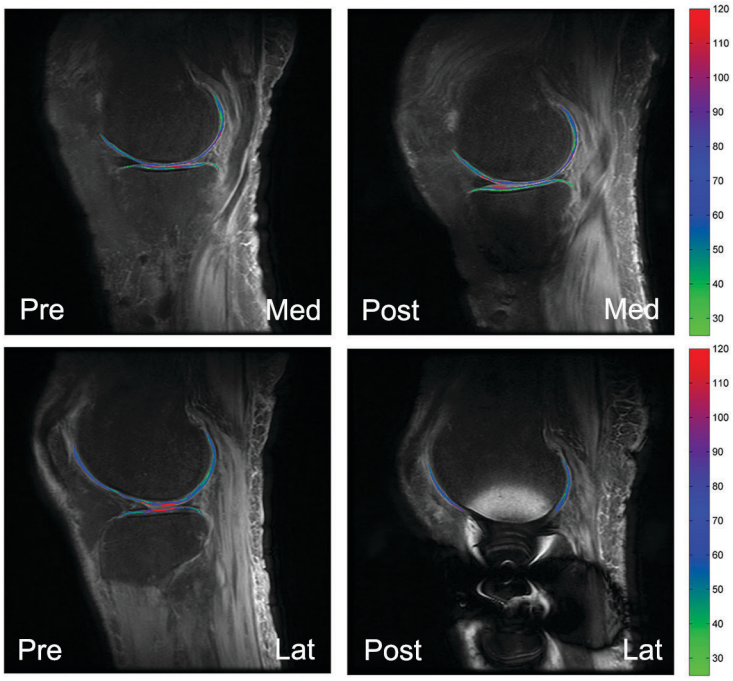
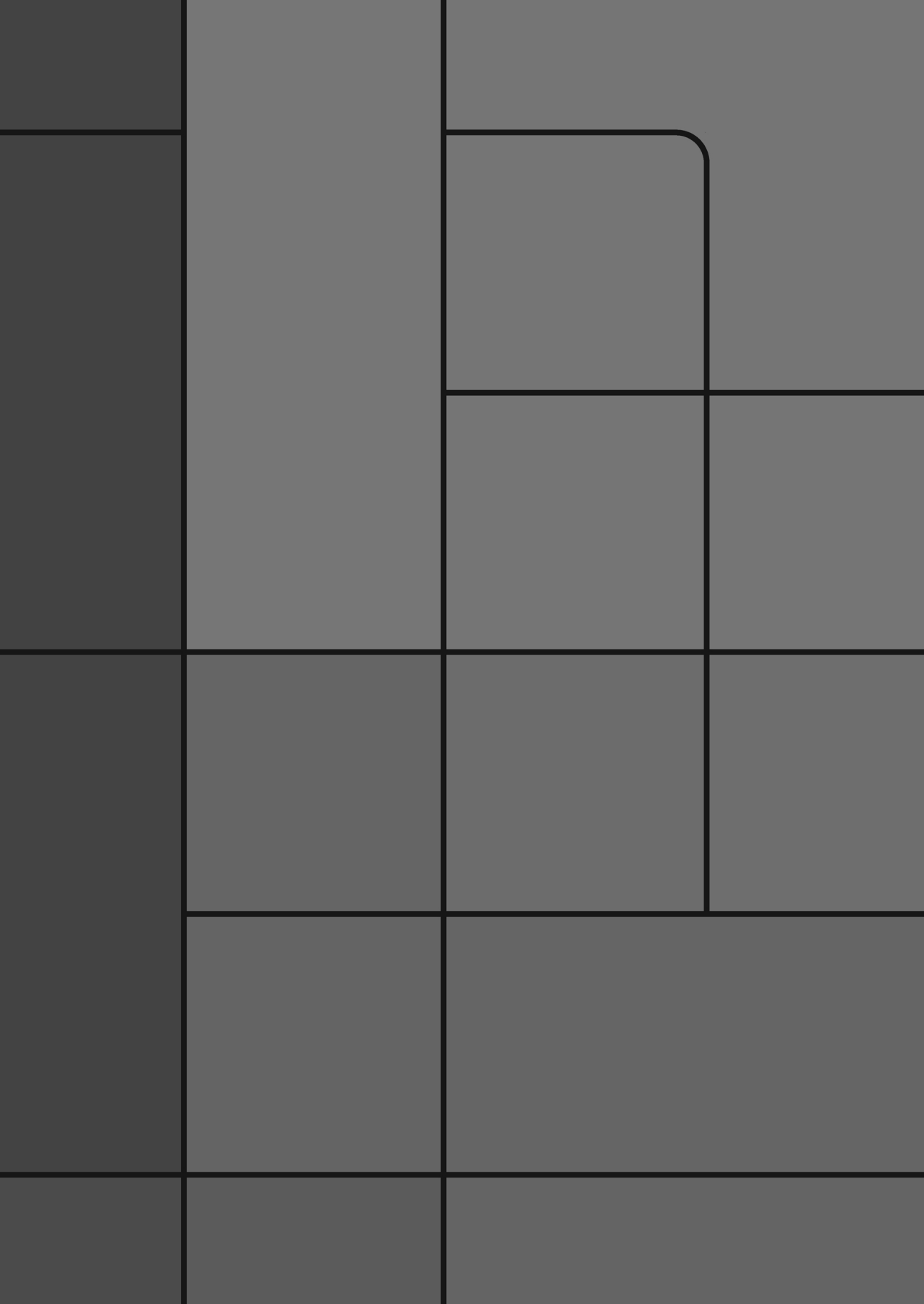


Figure 4. Cartilage T2 color maps with and without the cobalt chrome staples on the T2 mapping sequence. No post-implantation color map is displayed for the lateral weight-bearing femoral and tibial cartilage as segmentation was not possible due to magnetic susceptibility artifacts. Pre, before implantation; Post, after implantation; Med, Medial compartment; Lat, Lateral compartment.



Chapter 7

Influence of delayed gadolinium enhanced MRI of cartilage (dGEMRIC) protocol on T2-mapping: is it possible to comprehensively assess knee cartilage composition in one post-contrast MR examination at 3 Tesla?

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Abstract

Objective:
To evaluate the possibility of assessing knee cartilage with T2-mapping and delayed gadolinium enhanced magnetic resonance imaging (MRI) of cartilage (dGEMRIC) in one post-contrast MR examination at 3 Tesla (T).

Design:
T2 mapping was performed in 10 healthy volunteers at baseline; directly after baseline; after 10 min of cycling; and after 90 min delay, and in 16 osteoarthritis patients before and after intravenous administration of a double dose gadolinium dimeglumine contrast agent, reflecting key dGEMRIC protocol elements. Differences in T2 relaxation times between each timepoint and baseline were calculated for 6 cartilage regions using paired t tests or Wilcoxon signed-rank tests and the smallest detectable change (SDC).

Results:
After cycling, a significant change in T2 relaxation times was found in the lateral weight-bearing tibial plateau (+1.0 ms, p=0.04). After 90 min delay, significant changes were found in the lateral weight-bearing femoral condyle (+1.2 ms, p=0.03) and the lateral weight-bearing tibial plateau (+1.3 ms, p=0.01). In these regions of interests (ROIs), absolute differences were small and lower than the corresponding SDCs. T2-mapping after contrast administration only showed statistically significantly lower T2 relaxation times in the medial posterior femoral condyle (-2.4 ms, p<0.001) with a change exceeding the SDC.

Conclusion:
Because dGEMRIC protocol elements resulted in only small differences in T2 relaxation times that were not consistent and lower than the SDC in the majority of regions, our results suggest that T2-mapping and dGEMRIC can be performed reliably in a single imaging session to assess cartilage biochemical composition in knee osteoarthritis (OA) at 3 T.

Introduction

Osteoarthritis (OA) is currently diagnosed based on clinical and radiographic criteria.[217] Unfortunately, conventional radiography, which visualizes cartilage indirectly, detects only late stages of degeneration. Novel magnetic resonance imaging (MRI) methods enable quantification of cartilage biochemical composition and microstructure. These quantitative MRI techniques are increasingly used in OA research, because they can detect early biochemical cartilage changes that precede morphological cartilage loss visible on conventional MRI.[88] The two most important cartilage components, glycosaminoglycans and collagen, can be determined with different quantitative MRI techniques. Because glycosaminoglycan content depletion and collagen integrity degradation occur at different stages of OA, quantification of both components is critical for comprehensive assessment of biochemical composition and structure of articular cartilage in early OA.[218]

Two widely used and validated quantitative MRI techniques are delayed gadolinium enhanced MRI of cartilage (dGEMRIC) to measure proteoglycan content and T2-mapping to assess collagen network integrity.[88] Non-contrast alternatives for dGEMRIC are poorly correlated to glycosaminoglycan content (T1rho) or require advanced MRI hardware (gagCEST and sodium MRI).[88, 91] A recent validation study showed a strong correlation of dGEMRIC with sulphated glycosaminoglycan content.[91] Thus, a combination of dGEMRIC and T2-mapping currently is an appropriate strategy for comprehensive assessment of biochemical composition of cartilage with MRI.[112] dGEMRIC requires intravenous administration of gadolinium dimeglumine (Gd-DTPA2-) contrast agent, exercise to enhance contrast agent distribution, and a delay between contrast administration and image acquisition of 1-2 hours.[219] As T2-mapping is acquired without any preparation, current practice is to acquire the techniques in separate MRI scan sessions pre- and post-contrast. Consequently, performing both techniques is costly, time-consuming, and difficult to implement in large clinical trials or clinical practice. Combining dGEMRIC and T2-mapping in a single scanning session would greatly improve the feasibility of comprehensive quantitative MRI assessment of cartilage, but requires knowledge of possible influences of dGEMRIC-specific protocol issues on T2 relaxation times. Therefore, we aimed at assessing the influence of different elements of our dGEMRIC protocol, i.e. contrast agent, cycling, and delay, on T2 relaxation time of knee cartilage. Our hypothesis was that dGEMRIC protocol elements do not influence T2 relaxation times and that dGEMRIC and T2-mapping can be performed in one scanning session.

Methods

Population

Two different groups of participants were used in this crosssectional study. Approval from the Institutional Review Board of Erasmus MC (MEC 2014-096 and MEC-2012-218) and written informed consent was obtained from all participants. The study was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2000.

The influence of cycling and delay between hypothetical contrast administration and image acquisition was studied in 10 healthy volunteers without history of severe knee injury or specific knee disorder (5 males, mean age 24 years (SD (Standard Deviation) 2.1), average body mass index (BMI) of 23.5 kg/m2 (SD 2.9)).

The influence of contrast agent was studied in 16 OA patients (6 males, 9 right knees) mean age 62.9 years (SD 6.4), average BMI 30.6 kg/m2 (SD 5.0)) on the waiting list for total knee arthroplasty, recruited from the outpatient clinic of the Department of Orthopedic Surgery of Erasmus MC Rotterdam between October 2012 and December 2015. The inclusion criteria were radiographic knee OA (Kellgren-Lawrence grade ≥ 1).[69] Patients were excluded when they had renal insufficiency (glomerular filtration rate <60 mL/min), a history of previous reactions to MR contrast agent, or were physically unable to cycle. The medial knee compartment was most affected in 12 patients, the lateral compartment in the other 4.

MRI acquisition

All subjects were scanned on a 3 Tesla (T) MR system (Discovery MR750; GE Healthcare, Milwaukee, WI, USA) with a dedicated eight-channel transmit and receive knee coil (Invivo, Gainesville, FL, USA). T2-mapping was performed using a 3D fast spin echo (FSE) sequence with 5 echo times (3, 13, 27, 40, 68 ms); 3 mm slice thickness; and in-plane resolution of 0.5x0.8 mm.[166] Scan time was approximately 9:40 minutes. A 3D high-spatial-resolution fat-saturated fast spoiled gradient-echo (FSPGR) sequence was also acquired for cartilage segmentation (Appendix).

In the healthy volunteers, T2-mapping of the left knee was performed 4 times (Appendix). First, a baseline scan was made, followed by a second scan directly afterwards (without repositioning the subject); a third scan 70 minutes after baseline following 10 minutes of cycling; and a fourth scan 90 minutes after baseline. The second scan was used to determine the reproducibility of T2-mapping. Except for 10 minutes of cycling, the subjects did not load their knee during the total examination.

The participants with OA underwent our complete dGEMRIC protocol. This involves intravenous administration of 0.2 mmol/kg Gd-DTPA2- (Magnevist; Bayer Schering, Berlin, Germany), 10 minutes of cycling at intermediate pace on an exercise bicycle, and a delay of 90 minutes, before image acquisition using a 3D inversion-recovery non-fat-saturated

spoiled gradient-echo sequence with five different inversion times (Appendix).[91] The baseline T2-mapping scan was performed 20 minutes before contrast administration. Post-contrast T2-mapping was done 60 minutes after contrast administration directly preceding dGEMRIC acquisition, reflecting the most efficient strategy when the two techniques are to be combined in a single imaging session without lengthening total examination time.

Image processing

Post-processing was performed using an in-house developed Matlab (R2011a; Math-Works, Natick, MA, USA) extension that incorporates automated rigid registration in 3D for motion compensation.[167] Full-thickness cartilage masks were manually segmented on 7 slices with 3 mm interval on the FSPGR sequence. Six cartilage regions of interest (ROI) were selected corresponding to the weight-bearing and posterior femoral condyles and tibial plateaus, both in the medial and lateral knee compartment. 'Weight-bearing' was defined as the cartilage within the outer perimeters of the menisci. The posterior ROIs consisted of the femoral cartilage behind the posterior meniscal horns. The acquired T2-mapping scans were registered to the FSPGR sequence to ensure exact matching of ROIs. Within each ROI, mean T2 was computed using a weighted averaging procedure.[167]

Statistical analyses

Data was tested for normal distribution using the Shapiro-Wilk method. Paired t-tests and Wilcoxon-Signed-rank tests were used for each cartilage ROI to compare T2 relaxation times made following the dGEMRIC protocol aspects with the baseline scans. A p-value <0.05 was considered statistically significant. To assess the reproducibility of our T2-mapping MRI technique, we calculated the smallest detectable change (SDC), defined as the smallest amount of measurable change which cannot be attributable to measurement error. A change larger than the SDC exceeds the limits of agreement as defined by Bland and Altman. The formula for calculating the SDC is 1.96 * √2 * Standard Error of Measurement (SEM).[220] The SEM needs to be calculated from a test-retest experiment in a stable population. It was derived from the first two measurements in the healthy population. The SEM was defined as the SD of the difference between the two scans divided by the square root of two (SDdifference/√2).[220] All analyses were performed using SPSS 21.0 (IBM Corp, Armonk, NY, USA).

Results

Mean T2 relaxation times and differences between scans for both groups are displayed in Table I and II. The SDC derived per ROI from the first two scans in the healthy population ranged from 1.0 to 2.7 ms. Between the baseline scan and post-cycling scans in the healthy volunteers, a statistically significant difference (+1.0 ms, p=0.04) in the lateral weight-bearing tibial plateau was found. After 90 minutes delay, statistically significant differences between scans were found in the lateral weight-bearing femoral condyle (+1.2 ms, p=0.03) and lateral

weight-bearing tibial plateau (+1.3 ms, p=0.01). In the OA population, paired *t* tests and Wilcoxon-Signed-rank tests revealed a statistically significant difference (-2.4 ms, p<0.001) in the medial posterior femoral condyle between pre- and post-contrast MRI scans. Other regions did not show statistically significant differences in T2 relaxation time.

Discussion

In this study on the influence of dGEMRIC protocol elements on T2 relaxation times of cartilage we found comparable T2 relaxation times acquired before and after cycling, delay, and administration of contrast agent and no statistically significant differences in the majority of regions. The observed range of T2 relaxation times of both healthy volunteers and OA patients is consistent with values previously published, but we observed a relatively large spread in SDC between ROIs.[88] Ten minutes of cycling statistically significantly increased T2 relaxation times in the lateral weight-bearing tibial plateau. After 90 minutes delay a statistically significant T2 relaxation time increase in the lateral weight-bearing femoral condyle and lateral weight-bearing tibial plateau was found. The complete dGEMRIC protocol including contrast agent statistically significant lowered T2 relaxation times in the medial posterior femoral condyle of OA patients. However, absolute differences in T2 relaxation times were small and there was no trend towards higher or lower values after one of the protocol aspects. The statistically significant differences after cycling, delay and contrast agent did not appear consistently in the same ROI. Furthermore, the observed differences between the baseline scans and the scans after cycling and 90 minutes delay were lower than the corresponding SDCs, indicating that the difference may be attributed to chance. In the OA population, the difference between scans in the posterior medial femoral condyle exceeded the SDC. However, the SDC was only calculated in healthy volunteers and it is questionable whether this SDC can be fully translated to the OA population. The reason why the posterior medial femoral condyle was the only region to show a statistically significant difference and exceeded the SDC needs further investigation. Based on baseline T2 relaxation times and radiographs, this region did not show more advanced OA than the other medial regions. Due to multiple testing, the observed significant difference in only one or two regions might be explained by type I error. We did not correct for multiple testing as this might obscure possible effects of dGEMRIC protocol aspects. Unfortunately, no comparative previous literature is available regarding the influence of cycling at an intermediate pace on T2 relaxation times. Regarding the delay, we believe that our results are consistent with previous research in which T2-mapping was performed repeatedly within one scanning session or with a 9 hours interval, showing no statistically significant differences in T2 relaxation times.[111, 221] Contrary to our results regarding the influence of the contrast agent, Yoon et al. found significant lowering of T2 values in femoral cartilage.[222] The difference between their results and ours might be due to different T2 acquisition technique or magnetic field strength (1.5 T vs. 3 T). The type of exercise was also different, as patients walked for 15 minutes in their study. In a pilot study by Nieminen et al., however, no

effect of contrast agent on T2 relaxation times was found in three volunteers using a similar dGEMRIC protocol at 1.5 T.[223] Similarly, a recent study with 11 healthy volunteers found no relevant influence of intravenous gadolinium on T2 relaxation time of hip cartilage at 7 T.[224] A limitation of our study is that it was not powered sufficiently to exclude a possible effect of the dGEMRIC protocol elements based on the 95% confidence interval. To exclude a difference in a validation study based on equivalence, we would need at least 120 patients. Including this amount of patients for our research question is not feasible based on costs and load for patients. A second limitations is that we were unable to examine all dGEMRIC protocol elements separately in one population. The influence of contrast agent on T2 relaxation times of cartilage was not studied in healthy volunteers for ethical reasons. It was also impossible to test the influence of contrast agent without performing the cycling exercise and delay in image acquisition, because both are necessary for the contrast to reach the knee articular cartilage. In addition, the influence of cycling and delay in acquisition separate from the total dGEMRIC protocol was not studied in the OA population for feasibility reasons, because this would require over 5 hours of the patient's time. Therefore, the results of the influence of cycling and delay in image acquisition might not be generalizable to the OA population. A final limitation is that we did not acquire a test-retest T2-mapping scan in the OA population. In conclusion, our results suggest that T2-mapping can be performed reliably in combination with dGEMRIC acquisition in a single imaging session to comprehensively assess cartilage biochemical composition in knee OA at 3 T.

Tables

Table I. Mean T2 relaxation times and T2 differences of the measurements in healthy volunteers

	Baseline			Reproducibility scan			Post-cycling			Post-delay			Cycling - Baseline difference			Delay - Baseline difference			SDC
	Mean	SD	95% CI	Mean	SD	95% CI	Mean	SD	95% CI	Mean	SD	95% CI	Mean	95% CI	p	Mean	95% CI	p	
Weight-bearing femoral condyle																			
Lateral	39.0	2.7	37.1-40.9	40.3	3.2	38.0-42.5	39.6	2.2	38.0-41.2	40.2	2.8	38.2-42.2	0.6	-0.1 - 1.3	0.08	1.2	0.2 - 2.3	0.03	1.6
Medial	35.2*	2.0	33.7-36.6	35.4	2.0	34.0-36.9	35.2	1.7	34.0-36.4	36.0	2.1	34.5-37.5	0.0	-0.8 - 0.9	0.85**	0.8	-0.4 - 2	0.16**	1.7
Posterior femoral condyle																			
Lateral	33.1	2.0	31.6-34.6	32.6	1.7	31.4-33.6	32.7	1.8	31.3-34.0	32.9	1.8	31.6-34.1	-0.5	-1.2 - 0.3	0.21	-0.2	-0.9 - 0.5	0.48	1.1
Medial	34.9	1.5	33.9-36.0	34.8	1.3	33.9-35.7	34.3	1.4	33.3-35.3	34.4	1.2	33.5-35.3	-0.6	-1.4 - 0.2	0.11	-0.5	-1.3 - 0.3	0.19	1.0
Weight-bearing tibial plateau																			
Lateral	33.8	1.9	32.5-35.2	34.4	2.1	32.9-36.0	34.8	1.8	33.5-36.1	35.2	2.3	33.5-36.8	1.0	0.1 - 1.9	0.04	1.3	0.5 - 2.2	0.01	1.2
Medial	34.8	3.2	32.5-37.1	34.7	2.5	32.9-36.5	34.0*	1.6	32.8-35.2	34.5*	1.1	33.7-35.3	-0.8	-3.2 - 1.6	0.85**	-0.3	-2.7 - 2.1	0.92**	2.6

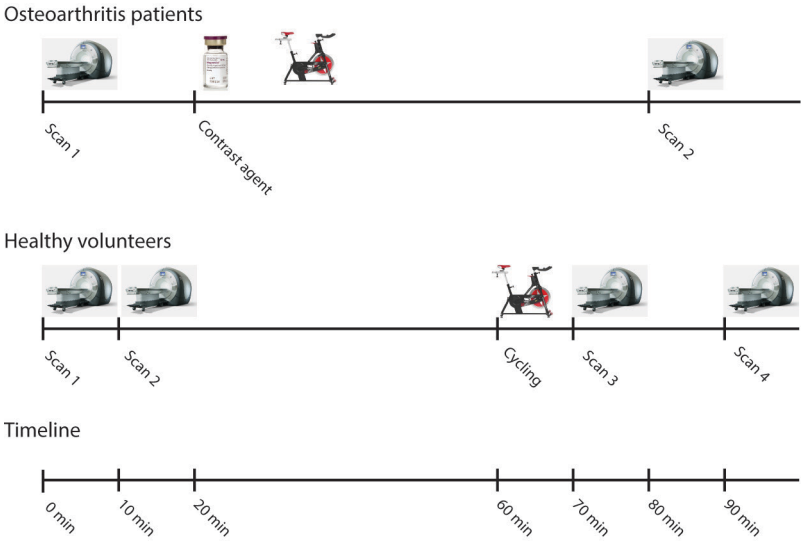
All values are milliseconds except for the p-values. SD: Standard Deviation; 95% CI: 95% Confidence Interval; SDC: Smallest Detectable Change
Statistical significance was tested using paired t-tests, values marked with an * did not show normal distribution and were tested using a Wilcoxon-Signed-Ranks test (**). As means and medians were very similar, we choose to also present means, SD and 95% CI for non-normally distributed data.

Table II. Mean T2 relaxation times and T2 differences of the measurements in the OA population

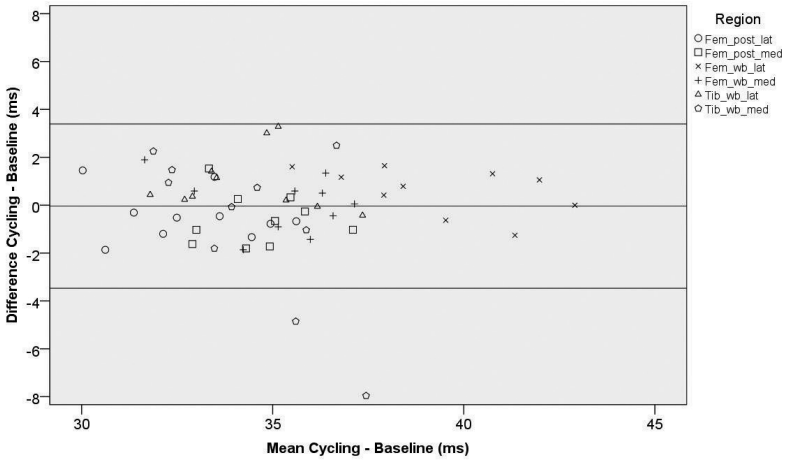
	Baseline			Post contrast administration			Difference			SDC
	Mean	**SD**	**95% CI**	**Mean**	**SD**	**95% CI**	**Mean**	**95% CI**	**p**	
Weight-bearing femoral condyle										
Lateral	38.5	3.7	36.5 - 40.5	38.3	3.8	36.2 - 40.3	-0.2	-2.1	0.65	1.6
Medial	42.5	4.7	40.0 - 45.0	43.7	7.2	39.9 - 47.6	1.3	-4.6	0.26	1.7
Posterior femoral condyle										
Lateral	39.8*	6.4	36.4 - 43.3	39.7*	4.9	37.1 - 42.4	-0.1	-4.2	0.98**	1.1
Medial	40.5	3.7	38.6 - 42.5	38.1	3.6	36.2 - 40.0	-2.4	-4.9	<0.001	1.0
Weight-bearing tibial plateau										
Lateral	37.9*	7.6	33.9 - 42.0	36.7*	6.8	33.0 - 40.3	-1.3	-2.7	0.09**	1.2
Medial	40.6	4.7	38.1 - 43.1	42.8	7.9	38.6 - 47.0	2.2	-5.0	0.08	2.6

All values are milliseconds except for the P-values. SD: Standard Deviation; 95% CI: Confidence Interval; SDC: Smallest Detectable Change (derived from first two MRI scans of healthy volunteers). Statistical significance was tested using paired t-tests, values marked with an * did not show normal distribution and were tested using a Wilcoxon-Signed-Ranks test (**). As means and medians were very similar, we choose to also present means, SD and 95% CI for non-normally distributed data.

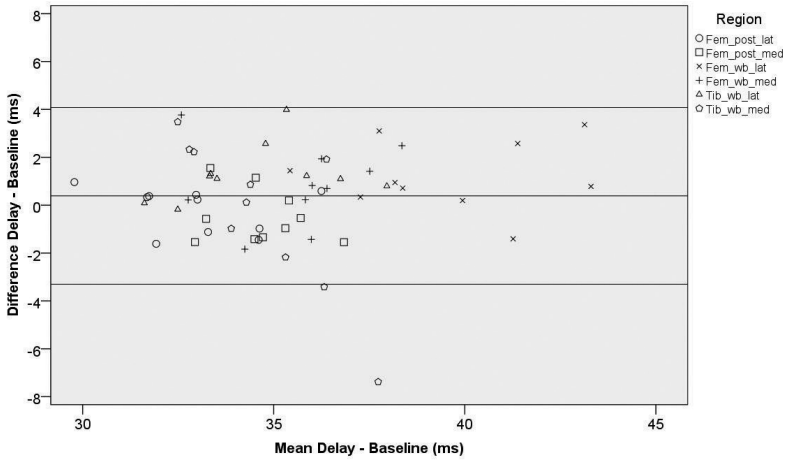
Appendix



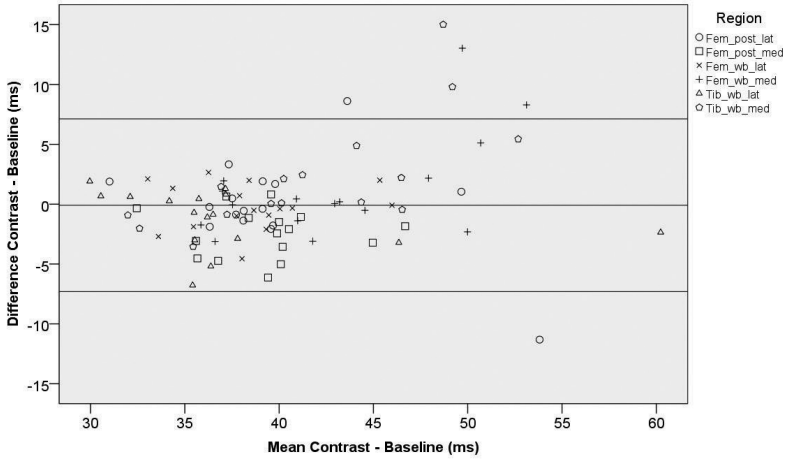
Supplementary Figure 1. Timeline of scan protocols for the OA patients and the healthy volunteers.



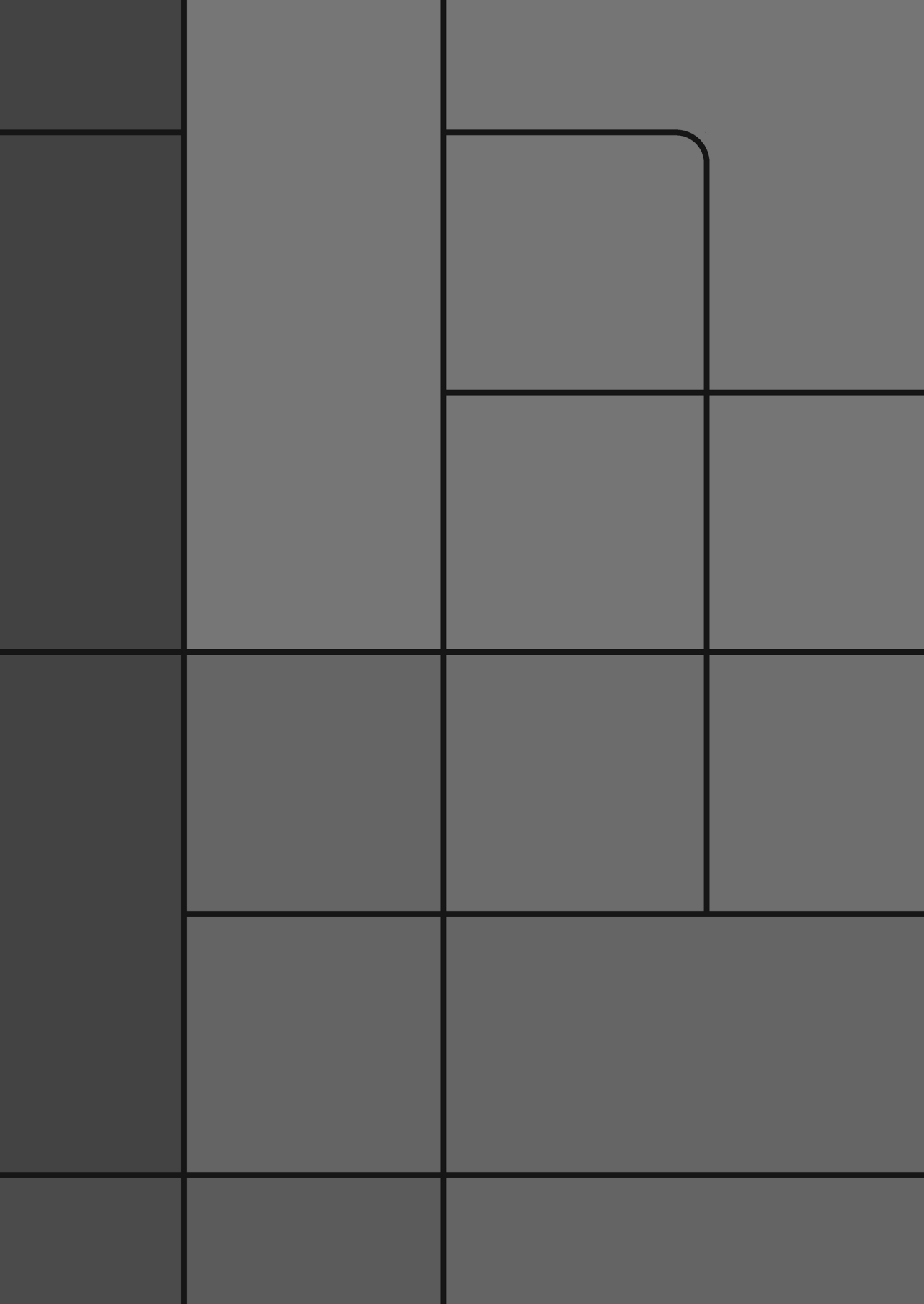
Supplementary Figure 2. Bland–Altman plot of differences between baseline and post-cycling scan.



Supplementary Figure 3. Bland–Altman plot of differences between baseline and post-delay scan.



Supplementary Figure 4. Bland–Altman plot of differences between baseline and post-contrast scan.



Chapter 8

General discussion

General discussion

In this thesis, the clinical results of an RCT are described comparing an unloading knee brace with a high tibial osteotomy HTO for patients with medial knee osteoarthritis and a varus knee malalignment. This study fills a critical knowledge gap, as no previous RCT compared these commonly applied non-operative and operative interventions. The clinical results revealed that an HTO is more effective in reducing knee pain than an unloader brace. These findings have clear implications for clinical practice, empowering both physicians and patients to make better informed treatment choices, especially when considering an invasive procedure like HTO with the associated risks. Conducting an RCT comparing non-operative and operative treatments presents several challenges, as described in the following paragraph of this discussion. Besides the comparison of two unloading therapies in terms of clinical outcomes, our study used advanced quantitative imaging techniques to determine their capability to detect the effects of two different unloading therapies on both cartilage and subchondral bone within a relatively short period of one year of follow-up. The development of these techniques has made significant progress over the last two decades. Initially, their development and application primarily focused on small groups of subjects and patients.[94, 160, 181, 183, 208, 225] Through this research, we have learned that these techniques are able to capture aspects of the osteoarthritis process before signs are visible on morphologic imaging techniques, like radiography and conventional MRI.[88, 93] The imaging outcomes of our RCT demonstrate that T2 mapping and quantitative SPECT-CT are also capable of monitoring the effect of unloading therapy. We showed that, with these techniques, changes in the composition of cartilage and subchondral bone can be detected within a relatively short period of time.[Chapter 3] This makes these techniques promising for large-scale clinical studies or clinical practice concerning osteoarthritis care. However, there are several challenges and considerations when moving from small-scale studies with a selected study population to large clinical trials or even clinical practice. These considerations are described in the second part of this discussion.

Practical challenges in conducting a randomized intervention study on medial knee osteoarthritis

In recent decades, there has been an increasing focus on conducting high-quality scientific research, with RCTs serving as the gold standard for prospective studies.[226, 227] Numerous laws, guidelines and regulations have been established to ensure that research involving patients adheres to ethical and methodological standards.[228-230] The Osteoarthritis Research Society International (OARSI) has provided recommendations for conducting clinical studies on osteoarthritis.[231, 232] These recommendations include the use of a parallel two-group randomized controlled trial, block randomization, stratification, blinding, and the use of valid, reliable and responsive patient-reported outcome measures (PROMs), all of which were implemented in our RCT. However, the rigid nature of such a trial design posed several practical and methodological challenges. In our study, certain factors led to difficulties with patient recruitment. First, a number of patients had a clear preference for one of the two treatments under investigation. Various reasons for this preference were reported, including the long duration of their knee complaints and the multiple conservative treatment attempts they had undergone. In some patients, such experiences led them to perceive that a surgical intervention was the only viable option. Furthermore, the manner by which information was provided by the treating orthopedic surgeon may have influenced the patients' treatment preferences.[233] Finally, we recruited patients from clinics that had a dedicated HTO surgeon. A substantial number of patients was specifically referred to these centers for an HTO by general practitioners or other orthopedic surgeons. These patients were generally no longer willing to undergo conservative treatment with a brace. Another issue that led to difficulties in patient recruitment was the reluctance of patients, but also of the treating surgeons, to the process of randomization due to fundamental differences between the two treatment options. This phenomenon is also seen in other studies comparing operative and non-operative treatments.[234, 235] Geographical accessibility also posed a significant hurdle for patient recruitment. At our study's initiation, two clinics in the Netherlands conducted the majority of HTOs in the country. Both participated in the trial. One of these clinics was located in the northeastern part of the country, while the coordinating clinic was situated in the southwestern region. All patients had to travel twice to the coordinating clinic for the quantitative imaging. As a result, some patients faced journeys of over 200 kilometers for a one-way trip, which is a substantial distance by Dutch standards. Consequently, the travel distance discouraged some patients from participating. This issue underscores the importance of multicenter imaging, a concept elaborated on later in this discussion. Another challenge for our study was that after the study commenced, the other high-volume clinic ceased operations due to a hospital merger. Consequently, the HTO-performing surgeons from this clinic dispersed to various other hospitals. Unfortunately, it took a considerable amount of time to start the study in all of these clinics. As a result, we expanded the study from initially involving four clinics to encompassing nine clinics by the study's conclusion. An additional reason for engaging more clinics in the study was the decline in the use of HTO as a treatment for medial knee osteoarthritis in the Netherlands. This mirrors the global

trend showing a clear increase in the utilization of (unicompartmental) knee arthroplasty in favor of HTO.[58, 236, 237] The above-mentioned challenges contributed to slower patient recruitment and may have led to the inclusion of a select group of patients who were willing to participate despite the above-mentioned obstacles. Another obstacle for our study was the delay in treatment initiation. Despite the predetermined agreement that patients would start treatment as soon as possible, delays were encountered. In cases of HTO, it was agreed that patients would undergo surgery within two months. However, hospital waiting lists and patient preferences occasionally hindered timely surgical intervention. This was generally less of an issue for the brace treatment. However, one health insurer was reluctant to reimburse the brace treatment, despite the fact that the treatment was included in a framework agreement for basic insured care of the Dutch National Healthcare Institute. This reimbursement issue contributed to a delay in the initiation of brace treatment in certain patients. A methodological issue we faced in our trial was blinding. Ideally, we would have applied blinding for intervention in our study. Theoretically, we could have implemented a double dummy trial design with a sham operation and a brace without unloading capabilities, but applying this in a credible way would be almost impossible. This would probably have resulted in a greater placebo effect of the HTO operation than that of the brace, as surgical procedures to tend to have a greater placebo effect.[158, 238, 239]

The above mentioned challenges collectively underscore the reality that adhering strictly to ideal scientific guidelines in research is not always feasible. In these circumstances, pragmatic solutions must be sought, necessitating compromises. In our study, we opted not to differentiate between opening wedge and closing wedge HTO as previous research did not find one of these techniques to be superior.[132, 159, 240] Additionally, due to the limited number of potential participants from high-volume centers, we engaged multiple clinics with lower HTO volumes in our research. A major concession we had to make was to halt the study before reaching the intended number of patients from the initial power calculation. Given the slow pace of inclusion, it seemed an impossible task to reach the targeted sample size within the time frame of the research grant duration. Consequently, in consultation with the study's sponsor, we recalculated the required sample size using the standard deviation (SD) of the KOOS pain subscale (the primary outcome of the study) using the baseline data of our own study. This SD was much smaller than the SD used in the initial calculation and therefore led to a redefinition of the required sample size which was reduced by 50%. Despite the small sample size, we were able to identify an unequivocal clinically relevant difference between the two treatments. Therefore, the study clearly makes a contribution to our knowledge on unloading therapy for patients with medial knee OA. Making the concession to end a study prematurely becomes a pragmatic necessity when patient inclusion poses significant challenges. In hindsight, one potential solution to enhance inclusion of patients in our study would be to use a different study design like cluster randomization, to recruit patients from primary healthcare settings, such as general practitioners or physical therapists or to use propensity matching of prospective cohort studies.[60, 241]

Challenges in implementing quantitative imaging in clinical studies of knee osteoarthritis

In recent years, there has been significant consideration regarding the use of quantitative imaging in clinical studies on osteoarthritis. Various scientific committees have published reviews and held consensus meetings with experts to formulate guidelines in this regard.[65, 242] For instance, the Radiological Society of North America (RSNA) established the Quantitative Imaging Biomarker Alliance (QIBA) with the goal of enhancing the utility and practicality of quantitative imaging biomarkers in clinical research and practice.[243, 244] The QIBA defines 'profiles' regarding the use of quantitative imaging as a biomarker. These profiles provide guidance on what needs to be achieved when using quantitative imaging. The QIBA recently defined a profile for MRI-based compositional imaging of knee cartilage.[79] In their recommendations significant emphasis is placed on the standardization of scanning protocols when using quantitative MRI in a multicenter setting. The rationale for this is that quantitative MRI results depend on the equipment manufacturer, field strength, acquisition protocols and analysis tools and therefore cannot be directly compared. However, multicenter studies on osteoarthritis are generally driven by clinicians in the fields of orthopedic surgery or rheumatology and not by radiologists or manufacturers of imaging devices. Moreover, imaging in these studies is often a secondary outcome measure and therefore does not determine the choice for involving clinics that use the same scanning equipment. Furthermore, quantitative MRI measurements typically require lengthy scan times, posing challenges for patient comfort and resource allocation. Commercial interests may interfere with the desire to perform research and can impose constraints on scanning time. This potentially compromises the feasibility of integrating quantitative imaging with sufficient quality into the scanning protocol. Therefore, in reality the application of quantitative imaging in a multicenter setting is likely to result in a variety of imaging equipment from different vendors, each with their own implementation of quantitative MRI techniques. Opting to conduct all imaging in a single center might discourage patient participation due to the previously mentioned travel distance concern. It potentially also introduces selection bias since more ambulant patients are likely to be more willing to travel longer distances. A higher level of participation in our study could likely have been achieved if standardized quantitative MRI measurements were feasible in every hospital or, at the very least, in every region of the country. In summary, there is a clear need for reliable multicenter quantitative imaging. However, the above mentioned practical concerns indicate that standardization is not an easy task. Instead of deciding not to use quantitative imaging as an outcome measure in clinical studies when harmonization is not possible, we believe it is preferable to still make an effort to use these techniques, albeit with concessions. When faced with a variety of imaging equipment in your multicenter study, it is important to investigate whether there are differences between scans made with different equipment, what the magnitude of these differences are and whether they are systematic. To date, limited attention has been given to this approach in the literature. In our own multicenter multivendor study, we observed differences in T2 values among different scanning equipment but found good to excellent

longitudinal reproducibility within each center.[Chapter 5] Although our study population was too small to assess systematic differences between centers, in vivo and phantom measurements revealed a consistent pattern of differences in T2 values across centers. Consequently, our results suggest that T2 mapping can be used in multicenter studies even with incompletely harmonized protocols, provided that repeated measurements for the study participant are conducted within the same center using the same equipment.

Another challenge when implementing quantitative imaging in clinical studies is the potential influence of patient or disease characteristics, as well as treatment-related factors, on the feasibility and reliability of these measurements. An example of treatment-related factor in our RCT was that half of the patients underwent knee surgery involving metal implants. This raised concerns about the impact of HTO fixation materials on quantitative T2 mapping outcomes. Our study using human cadavers showed that accurate T2 mapping after a HTO procedure is possible, as long as there is no visual distortion of the region of interest (ROI).[Chapter 6] Human cadavers were used for this study given the possibility of performing a T2 mapping scan directly before and after the implantation of the material. Accurate T2 mapping after a HTO procedure was possible in all ROIs after implantation of a titanium fixation device and in most ROIs after implantation of a cobalt chrome fixation device. The same titanium and cobalt chrome implants were used in our RCT. In our RCT, we noticed more visual distortion, mainly of the tibial ROIs, which resulted in registration errors requiring manual segmentation, or making it even impossible to analyze these ROIs. Most likely, this was caused by the implanted material being closer to the joint surface in these cases. In our cadaver study, we made sure that the implanted material was a least 1 cm below the joint surface, which is accordance to the suggested surgical technique by the implant manufacturers.[245] Thus, although our cadaver study demonstrated the feasibility of accurate T2 mapping after HTO, the results of our RCT show that this is not directly applicable to daily practice, as the surgical guidelines are not always strictly adhered to. Patient demographics and disease characteristics add another layer of complexity. Factors such as age, body mass index (BMI), and injury history can introduce variability in quantitative MRI outcomes.[177, 181, 184, 185] To date, mainly selected populations based on specific knee conditions, age or a risk profile for osteoarthritis have been used in studies of quantitative imaging of knee cartilage.[99, 195, 246, 247] Our study using an unselected clinical population of outpatient orthopedic patients demonstrates that T2 relaxation times are age, BMI, and injury-dependent.[Chapter 4] It emphasizes the importance of accounting for these factors when conducting T2 mapping in an clinical population.

When starting this research project, we had access to various quantitative MRI techniques for cartilage assessment. These included T2 mapping, T1rho mapping and dGEMRIC. These techniques are readily accessible and applicable on standard 1.5 Tesla (T) and 3 T MRI scanners. They had also been previously employed to evaluate treatment effects on knee cartilage disorders.[100-107] Earlier research had indicated that T2 mapping exhibited a strong correlation with collagen content, while dGEMRIC, a commonly used technique in

osteoarthritis research at that time, showed a robust correlation with glycosaminoglycan (GAG) content.[87, 88, 248, 249] In dGEMRIC, as the name suggests, a contrast agent is introduced, either intravenously or intra-articularly. This agent needs to be administered 90 minutes prior to the scan to allow for diffusion into the knee articular cartilage. T1rho is a MR sequence that is believed to be correlated with GAG content that does not require contrast. However, at the time of initiation of our research project, a study conducted by our own research group revealed that T1r relaxation times did not correlate with cartilage GAG content.[91] Consequently, we decided not to use this technique as an outcome measure in our studies. It should be noted that recent publications suggest that T1rho may serve as a valuable measure of cartilage degeneration after all, with evidence suggesting that T1rho levels are more closely correlated with collagen degeneration than GAG depletion.[250, 251] Combining techniques that measure different aspects of the cartilage composition provides a more comprehensive assessment of the osteoarthritis status.[92, 111, 112] The combination of T2 mapping and dGEMRIC, however, posed a practical challenge because dGEMRIC requires a contrast agent while T2 mapping does not. Due to uncertainties about the impact of the contrast agent on T2 mapping, it was customary to conduct these two scans in separate sessions.[91, 112] This involves first performing a T2 mapping scan, followed by administering the contrast agent, and then conducting the dGEMRIC scan after the 90-minute waiting period. The total process takes nearly 3 hours, which proved to be a significant inconvenience for both patients and hospital resources. As we anticipated the inclusion of patients from various regions who often had to travel long distances, we did not want to burden them with such a lengthy scan protocol. For this reason, we decided not to include dGEMRIC in the scan protocol of our RCT. At the time, there was limited attention in the MRI research community to optimize scan protocols for the combined use of such imaging techniques. Consequently, we initiated our own study to investigate the influence of the dGEMRIC protocol on T2 mapping.[Chapter 7] The results demonstrated that T2 mapping and dGEMRIC could be reliably conducted within a single imaging session, which shortens the scan protocol and avoids the logistical challenge of scheduling two scan sessions at a specific time interval. This opens the door to future research aimed at comprehensive assessment of articular cartilage composition without compromising patient convenience and hospital resources.

By omitting T1rho and dGEMRIC, T2 mapping was the quantitative imaging technique primarily used in our studies. The T2 mapping technique utilized in our research was capable of revealing group-level differences.[Chapter 3- 5] However, the absolute differences in T2 relaxation times were small. In Chapter 7, we calculated the smallest detectable change (SDC) in T2 relaxation times of knee cartilage based on repeated measurements within a healthy population. This SDC ranged from 1.0 to 2.7 ms depending on the ROI. While the SDC was calculated in healthy volunteers and cannot be directly generalized to studies involving osteoarthritis patients, we frequently observed differences that did not exceed these values in our other studies.[Chapter 3, Chapter 4] Furthermore, since there is still no definition of normal or abnormal T2 values, the value of a technique like T2 mapping for the individual patient seems relatively small at this point and warrants further research, as will be discussed

later. The QIBA profile regarding MRI-based compositional imaging of knee cartilage states two claims on the use of T2 mapping in clinical studies.[79] Firstly, the average test-retest variability of T2 mapping is reported to be 4 to 5%. The 0.3 to 3.2% nonlongitudinal test-retest variability observed in our own research is well within that range.[Chapter 7] Secondly, the minimum detectable change (MDC) is reported to be a difference of 14% in T2 relaxation times. In our RCT, the differences in T2 relaxation times were less than 14% in the ROIs that showed a statistically significant difference. The QIBA profile states that clinical trials with larger sample sizes could potentially detect smaller differences, but no cut-off value is given for this necessary sample size. Another important note in the QIBA profile is that these claims require that the quantitative MRI measurements are performed on knee cartilage that has limited damage. Many of the studies featured in this dissertation present outcomes from patients with an advanced stage of cartilage wear, as the inclusion was based on radiographically apparent osteoarthritis. This group is ultimately not the population for which the use of these quantitative measurement methods is best suited.

In addition to the quantitative MRI methods available to us, several other promising techniques have been developed in recent years, such as chemical exchange saturation transfer imaging of GAG (gagCEST), sodium MRI, and Double Echo Steady State (DESS) MRI. Unfortunately, these techniques often require specific equipment, such as a 7T MRI scanner, or they are not commercially available. This makes it challenging to apply them in large-scale multicenter research or clinical practice. Furthermore, no single technique has demonstrated superiority.[88] In our scan protocols, alongside quantitative imaging methods, we also incorporated conventional morphological sequences. These sequences can be used for semi-quantitative analysis by manually scoring aspects of the osteoarthritis process, such as cartilage loss, meniscus and ligament degeneration, and bone marrow edema. Analyzing scans in this manner requires a significant time investment. An additional drawback is the fact that the applied surgical technique can be clearly seen on imaging. This makes a blind assessment more difficult, especially when you have to manually define regions of interest or do scores. There is ongoing development in this area, with possibilities to automate the analysis using machine learning. These developments could contribute to broader implementation in osteoarthritis research.[252] Since we have morphological scans available in all our studies at all time points, conducting a semi-quantitative analysis and exploring their relationship with quantitative measurements would be highly intriguing.

In our RCT on unloading therapies for medial knee osteoarthritis, we were able to incorporate quantitative SPECT-CT. It effectively detected changes resulting from the unloading therapy within a relatively brief time frame.[Chapter 3] Imaging techniques employing nuclear tracers offer compelling insights into osteoarthritis by revealing the current metabolic activity of the disease, rather than focusing on its structural damage as (quantitative) MRI does.[93, 94] This highlights the utility of combining diverse imaging modalities, creating a useful and complementary approach for monitoring osteoarthritis therapies.

Future perspectives

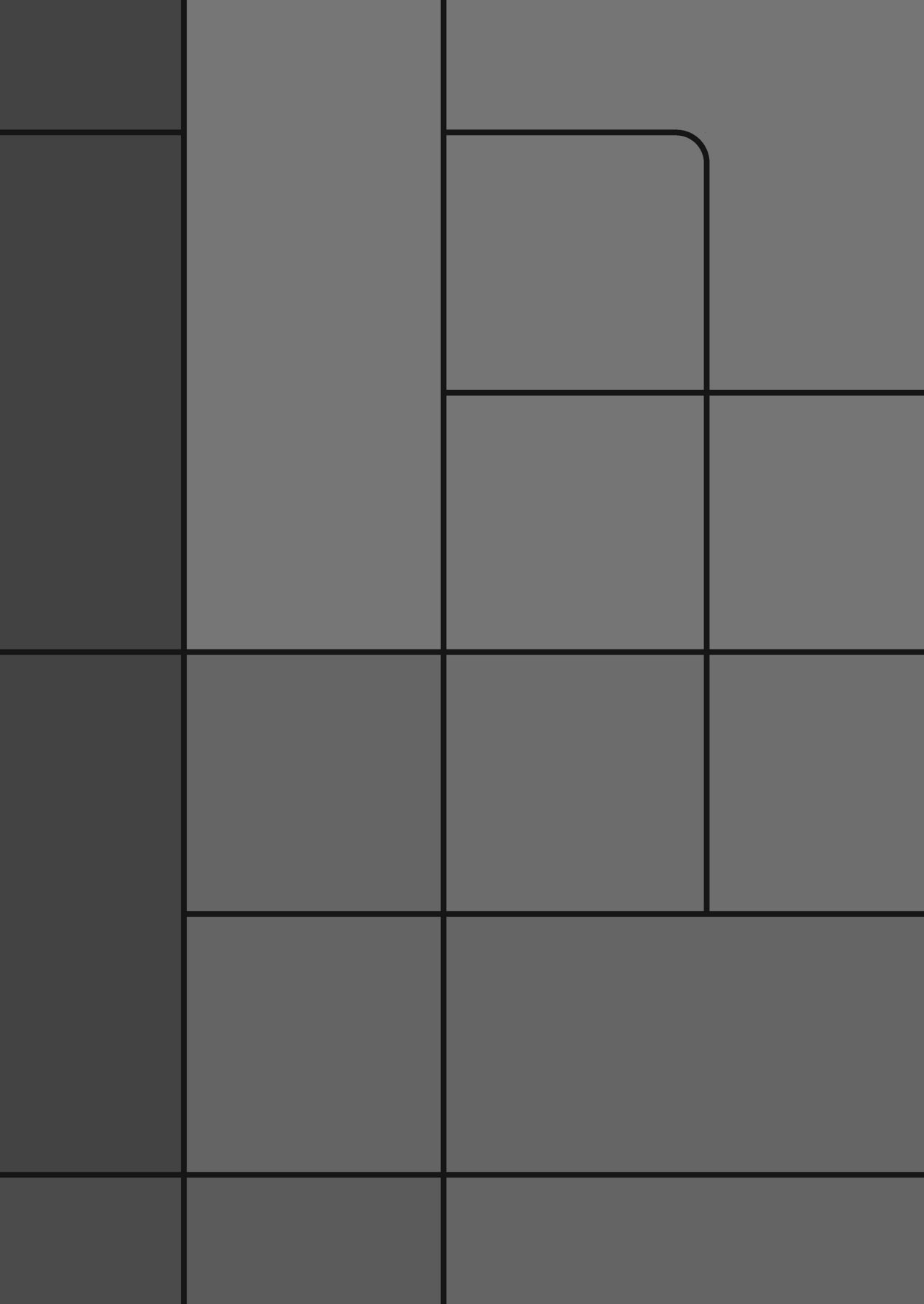
Looking ahead, despite all efforts to develop imaging techniques for early detection of cartilage damage and assessment of changes over time, there are currently no well-defined endpoints established. This hinders the widespread use of these techniques for evaluating osteoarthritis treatments and disease progression. This challenge is exacerbated by the multifactorial nature of osteoarthritis, characterized by its slow progression and poor correlation between disease onset and symptom manifestation. At present, total knee replacement is frequently chosen as the endpoint in knee osteoarthritis research. However, due to the slow progression of the disease, this is not a useful endpoint for assessing short-term treatment effects. Furthermore many other factors, such as socioeconomic status, play a role in the decision to undergo total knee replacement. The guidelines for osteoarthritis research from the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) cite radiography as a possible outcome measure.[63-66, 232, 253] However, it is well-established that radiography is not a responsive imaging technique and the osteoarthritis process is already in an advanced stage by the time it is visible radiographically. This limitation has posed a significant barrier to the investigation of disease-modifying osteoarthritis drugs (DMOADs) thus far. It is likely that these studies have often recruited inappropriate candidates due to the lack of suitable imaging methods to accurately determine the desirable stage of the osteoarthritis process and effectively assess study outcomes. Consequently, there is a clear need for surrogate markers.[254, 255] MRI appears to be promising in this regard due to the possibility of displaying the osteoarthritis process at an earlier stage.[63] However, for both quantitative and semi-quantitative MRI techniques, there are currently no defined normative or abnormal values. The challenge for the research community is to continue collecting biomarker data through clinical studies so that reliable surrogate endpoints can eventually be determined. The FDA's latest guidance document on osteoarthritis treatment development concludes with a statement welcoming all efforts to develop tools capable of better evaluating osteoarthritis treatments and to establish surrogate endpoints.[256] Fortunately, there are several initiatives underway to contribute to this goal. Various projects in the field of quantitative MRI for assessment of OA are currently working on defining normative data and cut-off values.[79] These initiatives also pay attention to the standardization of quantitative MRI sequences across different manufacturers.

The vast majority of osteoarthritis imaging currently focuses on morphology (radiography, conventional MRI) or composition (quantitative MRI).[81] Osteoarthritis has a gradual course with periods of little discomfort and periods of significant discomfort.[1] This variable course is not visible with imaging focused on morphology or composition. Therefore, there is growing interest in the assessment of functional and metabolic processes.[254] This is especially interesting for treatments aimed at specific osteoarthritis processes or osteoarthritis phenotypes, because the mechanisms of action of certain interventions can then be studied.[249, 257] Besides the SPECT-CT technique used in our RCT, various other techniques using nuclear tracer are currently being implemented in osteoarthritis research

including research projects that will use the highly advanced PET-MRI techniques.[258-260] This presents the opportunity to evaluate both the metabolic aspect and the structural damage of osteoarthritis in a single examination. It will be fascinating to see how these techniques can contribute to the development of good surrogate markers for osteoarthritis.

Another important topic for the widespread implementation of quantitative and semi-quantitative imaging is optimization of the image analysis. There is a need for user-friendly, efficient, and reliable quantitative image analysis tools. In our own studies, we had access to image registration for the MRI scans.[167] This ensured that we analyzed exactly the same ROI when evaluating scans made at different time points of the same patient. This was an important aspect of our measurement reliability. However, the segmentation of the cartilage ROIs had to be done manually by drawing masks on numerous slices of the MRI scan. This is a very time-consuming task. Therefore, there is a clear need for the use of (semi-)automatic segmentation. New technologies such as machine learning utilizing pattern recognition and artificial intelligence offer significant promise in this regard, potentially streamlining the image analysis process. There are already many initiatives from the research community in this regard.[252, 261-263] It would be beneficial if the commercial sector also recognizes the importance of developing good tools for quantitative imaging, as increased funding is likely to accelerate the development process.

Establishing surrogate markers and optimizing image analysis will be pivotal in releasing the full potential of quantitative imaging for improving the diagnosis and treatments for knee osteoarthritis. As we overcome the challenges and refine our approaches, we move closer to a future where quantitative imaging might play a central role in osteoarthritis care.



Chapter 9

Summary

Summary

Osteoarthritis of the knee is a significant burden for patients and society. Although osteoarthritis can manifest throughout the entire knee, the medial joint compartment is most commonly affected. When the lateral joint compartment remains relatively unaffected and there is a bowleg deformity, this presents opportunities for applying unloading therapy. In case of a bowleg, i.e. varus knee, malalignment, the majority of the load goes through the medial compartment of the knee. Unloading therapy aims to reduce the load on the medial compartment and shift it to the lateral compartment. Various conservative and operative unloading treatments are available for patients with medial knee osteoarthritis and a varus knee malalignment. Among these, a valgus unloader brace is an important conservative treatment, while high tibial osteotomy (HTO) is the primary operative treatment. Both therapies are frequently utilized in clinical practice. However, they have never been directly compared in a randomized study.

The main research project of this thesis is an open-labeled multicenter randomized controlled trial (RCT) that compares a valgus unloader brace with an HTO in patients with symptomatic medial knee osteoarthritis and a varus knee malalignment. The clinical results of this study are presented in **Chapter 2**. The primary outcome was knee pain after one year, measured with the pain subscale of the Knee injury and Osteoarthritis Outcome score (KOOS). A total of 51 patients were included in the study, of which 23 were randomized to the unloader brace and 28 to the HTO. The improvement in KOOS pain scores at 12 months follow-up for the brace group was 5.8 (95% CI: 2.0 to 9.5) and 34.6 (95% CI: 31.0 to 38.1) for the HTO group. The statistically significant difference in KOOS pain after 12 months between the unloader brace and HTO exceeded the minimal clinically important difference (MCID) for KOOS pain substantially. The KOOS pain at 24 months of follow-up and the other secondary outcomes measured with the numeric rating scale (NRS) for pain, other subscales of the KOOS, the Intermittent and Constant Osteoarthritis Pain score (ICOAP) and the Hospital for Special Surgery scale Knee Rating Scale (HSS) showed similar results. Therefore, this study suggests that on group level an HTO is more effective in reducing knee pain than an unloader brace.

In addition to clinical outcomes, our RCT studied changes in structural features of cartilage and subchondral bone after unloading therapy using advanced quantitative imaging techniques. Quantitative imaging techniques for knee osteoarthritis have seen significant development in the last two decades and have great potential in detecting osteoarthritis at an earlier stage, as well as monitoring osteoarthritis therapies. Especially in the field of magnetic resonance imaging (MRI), many techniques have been developed to assess the composition of the articular cartilage. In our study, we opted for the quantitative MRI technique T2 mapping, as it is well-validated and widely used in knee osteoarthritis research. T2 mapping uses transverse relaxation times to quantify the hydration content, collagen fiber orientation and collagen network integrity of articular cartilage. In recent years, there has

also been increasing attention on employing nuclear techniques like single photon emission computed tomography - computed tomography (SPECT-CT) to quantify the osteoarthritis process. SPECT-CT involves using a radioactive tracer attached to a bisphosphonate, which gets absorbed into regions with active bone metabolism. Subchondral bone metabolism is increased in osteoarthritic joints. We know that both T2 mapping and quantitative SPECT-CT are able to detect osteoarthritis in an earlier stage, as both articular cartilage deterioration and remodeling of the subchondral bone occur well before signs of osteoarthritis are visible on conventional radiography. However, their use for the assessment of the effects of osteoarthritis treatments have only been sparsely reported. In **Chapter 3**, we aimed to explore whether T2 mapping and quantitative SPECT-CT can detect early changes in knee articular cartilage composition and subchondral bone turnover after unloading therapy. The results showed that T2 relaxation times were statistically significantly increased in the lateral weight-bearing femoral and tibial regions in the HTO group at 12 months follow-up. The brace group showed statistically significantly increased T2 relaxation times of the medial weight-bearing femoral condyle. Maximum Standard Uptake Value (SUVmax) values were statistically significantly decreased at 12 months follow-up in the medial compartment in the HTO group. No changes were observed in the brace group. Both techniques showed statistically significant outcomes between the medial and lateral compartments. No correlation was observed between the change in T2 values and the change in SUVmax over time. We did not observe a correlation between the change of the quantitative imaging outcomes and the change in clinical outcomes as reported by the KOOS questionnaire. In conclusion, T2 mapping and SPECT-CT are able to detect changes after unloading therapy. Both techniques depict a different aspect of osteoarthritis. T2 mapping provides a measure for early structural damage, while SPECT-CT reveals the current metabolic activity of the disease. This makes both techniques complementary in monitoring osteoarthritis therapies. Our results suggest that HTO accomplishes a load transfer from the medial to the lateral compartment, while the valgus unloader brace does not.

The remaining chapters of this dissertation address practical challenges and considerations that arise when implementing quantitative MRI techniques, like T2 mapping, in a clinical study like our RCT on unloading therapy for medial knee osteoarthritis.

The group of patients affected by knee osteoarthritis displays substantial heterogeneity. The influence of factors like age, gender, body mass index (BMI), type of injury, duration of symptoms, and prior traumatic injuries on quantitative imaging results remains uncertain. Especially when quantitative imaging techniques are used in an unselected population. In **Chapter 4**, we therefore evaluated knee cartilage T2 relaxation times in a clinical population with knee complaints and its association with patients and disease characteristics and clinical symptoms. In this cross-sectional study, T2 mapping knee scans of 109 patients with knee pain who were referred for an MRI by an orthopedic surgeon were collected. T2 relaxation times statistically significantly increased with higher age and BMI. In patients with expected medial cartilage damage, the medial femoral T2 values were significantly higher

than the lateral, in patients with expected lateral cartilage damage the lateral tibial T2 values were significantly higher. A traumatic onset of knee complaints was associated with an acute elevation of T2 values. No significant association was found with clinical symptoms. Our study demonstrated age, BMI and type of injury dependent T2 relaxation times and emphasized the importance of acknowledging these variations when performing T2 mapping in a clinical population.

Another consideration is that studies into osteoarthritis treatment effects often necessitate large participant cohorts, frequently demanding multicenter studies. When applying quantitative imaging in these studies, an important concern is the variety of MRI scanner manufacturers and scanner models accessible in the market. In the context of MRI, factors such as field strength, coil type, and scan parameters notably influence quantitative imaging outcomes. Without knowledge of these influences, quantitative imaging techniques cannot be applied in multicenter studies. The purpose of the study described in **Chapter 5** was to determine the longitudinal reproducibility and multicenter variation of cartilage T2 mapping. Four healthy human subjects underwent T2 mapping twice at five different centers with a 6-month-interval. A phantom was scanned once at each center. Centers had various MRI scanners with different field strengths and T2 mapping acquisition protocols. We found that the intraclass correlation coefficients of the T2 mapping measurements per region of interest (ROI) and the ROI's combined ranged from 0.73 to 0.91, indicating good to excellent longitudinal reproducibility. Root-mean-square coefficients of variation ranged from 1.1% to 1.5% (per ROI) and 0.6% to 1.6% (ROIs combined) across the centers. A Bland-Altman plot did not reveal a systematic error. Evident, but consistent, discrepancies in T2 values were observed across centers, both in vivo and in the phantom. In conclusion, the results of this study suggest that T2 mapping can be used to longitudinal assess cartilage degeneration in multicenter studies. Given the differences in absolute cartilage T2 values across centers, absolute T2 values derived from various centers in multicenter multivendor trials should not be pooled.

When using quantitative MR imaging as an outcome tool in intervention studies, the treatment itself might conceivably exert influence on quantitative outcomes. In a treatment such as HTO, the introduction of metal implants raises questions about the reliability of performing quantitative imaging in the proximity of metal. In **Chapter 6**, we evaluated the possibility of performing T2 mapping after a HTO by assessing the extent of magnetic susceptibility artifacts and the influence on T2 relaxation times caused by two commonly used fixation devices. T2 mapping scans of 11 human cadaveric knee joints were made before and after implantation of a titanium plate and screws (n = 5) or cobalt chrome staples (n = 6). Due to the extent of the magnetic susceptibility artifacts, it was not possible to segment the knee cartilage and thus calculate T2 relaxation times in the lateral weight-bearing femoral and tibial cartilage regions only in the cobalt chrome group. In all cartilage regions of the titanium implanted knees and those unaffected by artifacts due to cobalt chrome implants, T2 relaxation times did not significantly differ between the two scans. Our

results suggest that accurate T2 mapping after an HTO procedure is possible in all areas after implantation of a titanium fixation device and in most areas after implantation of a cobalt chrome fixation device.

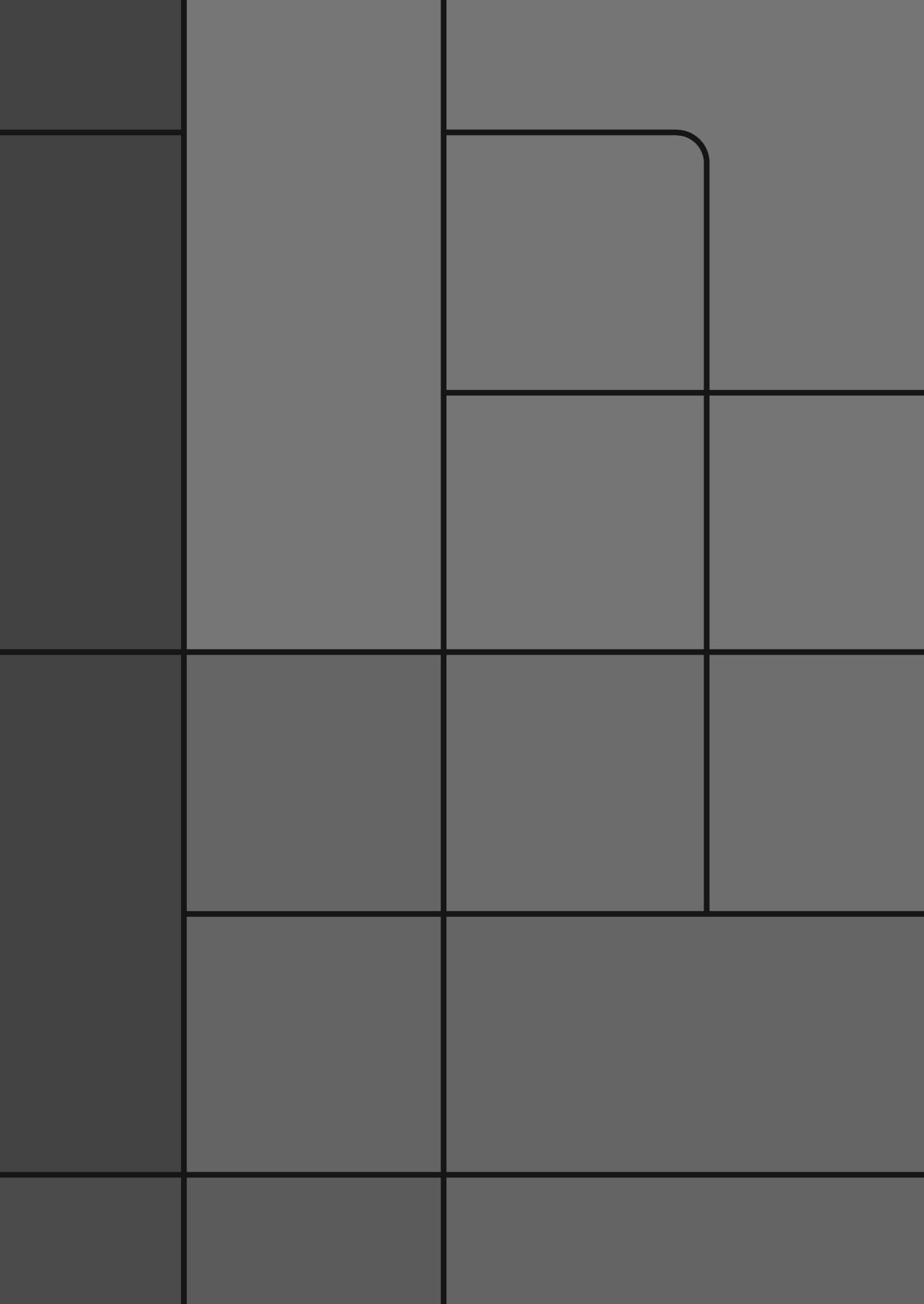
The final consideration involves the variety of MRI techniques available for assessing cartilage quality. Combining techniques that measure different aspects of the cartilage composition provides a more comprehensive assessment of the osteoarthritis status. Because some techniques use contrast agents and others do not, their combination typically involves multiple scanning sessions. This approach is time-consuming and lacks patient-friendliness. An ideal scenario would be to combine these different techniques within a single session. In **Chapter 7**, we explored the possibility of assessing knee cartilage with T2 mapping and delayed gadolinium enhanced MRI of cartilage (dGEMRIC) in one post-contrast MRI examination. In this study, T2 mapping was performed in 10 healthy volunteers at baseline; directly after baseline; after 10 min of cycling; and after 90 min delay, and in 16 osteoarthritis patients before and after intravenous administration of a double dose gadolinium dimeglumine contrast agent, reflecting key dGEMRIC protocol elements. The results showed a significant change in T2 relaxation times in the lateral weight-bearing tibial plateau after cycling. After 90 min delay, significant changes were found in the lateral weight-bearing femoral condyle and the lateral weight-bearing tibial plateau. In these ROIs, absolute differences were small and lower than the corresponding smallest detectable change (SDC). T2 mapping after contrast administration only showed statistically significantly lower T2 relaxation times in the medial posterior femoral condyle with a change exceeding the SDC. Our results suggest that T2 mapping and dGEMRIC can be performed reliably in a single imaging session to assess cartilage biochemical composition in knee osteoarthritis because dGEMRIC protocol elements resulted in only small differences in T2 relaxation times that were not consistent and lower than the SDC in the majority of regions.

Chapter 8 provides a general discussion of the research presented in this thesis, including the limitations and recommendations for further research. A major challenge for future research is to define normative or abnormal values for quantitative imaging techniques in order to create reliable surrogate markers. Another important topic for the widespread implementation of quantitative imaging in osteoarthritis care is optimization of the image analysis by creating user-friendly, efficient, and reliable quantitative image analysis tools.

Conclusions

The research outlined in this thesis enhances our understanding for making informed decisions regarding unloading therapy for patients with medial knee osteoarthritis. Additionally, it delves into crucial considerations essential for the successful application of quantitative imaging for early osteoarthritis detection and evaluating osteoarthritis intervention studies. The key findings can be summarized as follows:

- On group level, an HTO is more effective in reducing knee pain compared to an unloader brace in patients with medial knee osteoarthritis.
- Both T2 mapping and quantitative SPECT-CT are able to detect changes in articular cartilage and subchondral bone due to unloading therapy after a relative short period of time of only one year. Both techniques depict the osteoarthritis processes in a different way and are therefore useful and complementary for monitoring osteoarthritis therapies.
- T2 relaxation times are age, BMI and type of injury-dependent. It emphasizes the importance of acknowledging these influencing factors when performing T2 mapping in a clinical population.
- T2 mapping can be used to longitudinal assess cartilage degeneration in multicenter studies. Cartilage T2 values derived from various centers in multicenter multivendor trials should not be pooled given the differences in absolute T2 values across centers.
- Accurate T2 mapping after a HTO procedure is possible, as long as there is no visual distortion of the cartilage due to metal artifacts.
- T2 mapping and dGEMRIC can be performed reliably in a single post-contrast imaging session to assess cartilage biochemical composition in knee osteoarthritis.



Appendices

Nederlandse samenvatting

Knieartrose vormt een aanzienlijke last voor zowel patiënten als de maatschappij. Hoewel artrose zich door de hele knie kan manifesteren, wordt de binnenzijde van de knie, oftewel het mediale gewrichtscompartiment, het meest getroffen. Wanneer het buitenste (laterale) gewrichtscompartiment relatief onaangetast blijkt en er sprake is van een O-been biedt dit mogelijkheden voor behandelingen die het mediale compartiment ontlasten. In het geval van een O-been gaat het merendeel van de belasting namelijk door het mediale compartiment van de knie. Een O-been noemen we ook wel een varus beenas. Er bestaan diverse conservatieve en operatieve behandelingen voor mediale knieartrose met een varus beenas. Verscheidende therapieën hebben als doel de belasting van het mediale compartiment te verminderen en naar het laterale compartiment te verschuiven door het been richting een X-stand (valgus beenas) te bewegen. Een valgiserende brace is een belangrijke conservatieve behandeling, terwijl een valgiserende tibiakoposteotomie, beter bekend als 'high tibial osteotomy' (HTO), de primaire operatieve behandeling betreft. Beiden worden regelmatig toegepast in de klinische praktijk, maar zijn nog nooit direct vergeleken in een studie waarbij de behandeling voor de patiënt willekeurig wordt bepaald, een zogenaamde gerandomiseerde studie.

Het voornaamste onderzoeksproject van dit proefschrift betreft een gerandomiseerde studie (RCT) waarin een valgiserende brace werd vergeleken met een operatieve standscorrectie (HTO) bij patiënten met symptomatische mediale knieartrose in combinatie met een varus beenas. De klinische resultaten van deze studie worden beschreven in **hoofdstuk 2**. De primaire uitkomstmaat was kniepijn na één jaar, gemeten met de pijnschaal van de Knee injury and Osteoarthritis Outcome-score (KOOS). In totaal namen 51 patiënten deel aan de studie, waarvan 23 werden toegewezen aan de brace behandeling en 28 aan de HTO. Na 12 maanden was er een minimale verbetering in de KOOS pijnscores in de bracegroep, terwijl er een aanzienlijke verbetering was in de HTO groep. Dit verschil was beduidend groter dan het minimaal klinisch relevante verschil (MCID) van de KOOS pijnschaal. De KOOS pijnscores na 24 maanden en de andere secundaire uitkomsten, gemeten met de 'numeric rating scale' (NRS) voor pijn; andere subschalen van de KOOS; de Intermittent and Constant Osteoarthritis Pain-score (ICOAP); en de Hospital for Special Surgery Knee Rating Scale (HSS), toonden vergelijkbare resultaten. De uitkomsten van het onderzoek suggereren dat een HTO effectiever is in het verminderen van kniepijn dan een valgiserende brace.

Naast de klinische resultaten hebben we in de gerandomiseerde studie veranderingen in kraakbeen en subchondraal bot bestudeerd met geavanceerde kwantitatieve beeldvormende technieken. Subchondraal bot bevindt zich onder het kraakbeen. Kwantitatieve beeldvormingstechnieken voor knieartrose hebben de afgelopen twee decennia aanzienlijke ontwikkelingen doorgemaakt en maken het mogelijk om artrose in een vroeger stadium te detecteren en therapieën te monitoren. Met name op het gebied van MRI zijn er verschillende technieken ontwikkeld om de samenstelling van het gewrichtskraakbeen

te beoordelen. In onze studie kozen we voor de kwantitatieve MRI techniek T2 mapping omdat deze uitgebreid is gevalideerd en veel wordt toegepast in onderzoek naar knieartrose. De uitkomsten worden weergegeven in T2 relaxatietijden. T2 mapping geeft een kwantitatieve beoordeling van de hoeveelheid water en collageen in het kraakbeen. Beiden zijn belangrijke bestandsdelen van kraakbeen. De laatste jaren is er ook toenemend aandacht voor het gebruik van nucleaire technieken, zoals single photon emission computed tomography - computed tomography (SPECT-CT), om artrose te beoordelen. SPECT-CT maakt gebruik van een radioactieve tracer die is gekoppeld aan een bisfosfonaat welke wordt opgenomen in gebieden met actief botmetabolisme. Het botmetabolisme is verhoogd in gewrichten met artrose. We weten dat zowel T2 mapping als SPECT-CT in staat zijn om artrose in een vroeg stadium te detecteren omdat zowel de degeneratie van het gewrichtskraakbeen als de remodellering van het subchondrale bot plaatsvindt ruim voordat tekenen van artrose zichtbaar zijn op een röntgenfoto. Desondanks zijn deze beeldvormingstechnieken tot op heden nog maar sporadisch gebruikt om de effecten van artrosebehandeling te beoordelen. In **hoofdstuk 3** hebben we onderzocht of T2 mapping en kwantitatieve SPECT-CT vroege veranderingen in het kraakbeen en het subchondrale bot als gevolg van de valgiserende therapie kunnen detecteren. De bevindingen toonden aan dat T2 relaxatietijden statistisch significant toenamen in het laterale compartiment van de knie van de HTO-groep na 12 maanden. De brace vertoonde een statistisch significante toename van T2 relaxatietijden in het mediale deel van het femur. Als uitkomstmaat van de SPECT-CT gebruikten we de Maximum Standard Uptake Value (SUVmax). Deze waarden waren statistisch significant verminderd in het mediale compartiment van de HTO groep na 12 maanden. We zagen geen verandering van de SUVmax waarden in de brace groep. We vonden geen goede correlatie tussen de veranderingen in T2 waarden en de veranderingen in SUVmax in de loop van de tijd. Ook konden we geen goede correlatie aantonen tussen de beeldvormende technieken en klinische resultaten gemeten met de KOOS vragenlijst. Samengevat lieten onze resultaten zien dat T2 mapping en SPECT-CT in staat zijn veranderingen na ontlastende therapie te detecteren. Beide technieken belichten verschillende aspecten van artrose. T2 mapping biedt een maat voor vroege structurele kraakbeenschade en SPECT-CT geeft de huidige metabole activiteit weer van de ziekte in het subchondrale bot. De technieken vullen elkaar hierdoor aan bij het monitoren van artrosetherapieën. Onze resultaten suggereren bovendien dat HTO daadwerkelijk de belasting in de knie verschuift van het mediale naar het laterale compartiment terwijl de brace dit niet doet.

De overige hoofdstukken van dit proefschrift behandelen praktische uitdagingen en overwegingen die essentieel zijn voor de succesvolle toepassing van kwantitatieve MRI technieken, zoals T2 mapping, in een klinische studie zoals onze RCT over valgiserende therapie bij patiënten met mediale knieartrose. Deze overwegingen worden hieronder nader toegelicht.

De groep patiënten met knieartrose is zeer gevarieerd. De invloed van factoren op kwantitatieve beeldvormingsresultaten zoals leeftijd, geslacht, body mass index (BMI), type

letsel, duur van klachten en eerdere traumatische letsels blijft onzeker. Dit geldt voornamelijk bij het gebruik van kwantitatieve beeldvormende technieken in een populatie die niet is geselecteerd op specifieke kenmerken. In **hoofdstuk 4** hebben we daarom in een klinische populatie met knieklachten de relatie onderzocht tussen T2 relaxatietijden en patiënt- en ziektekenmerken en klinische symptomen. In deze studie werden 109 T2 mapping scans verzameld van patiënten met kniepijn bij wie op verzoek van een orthopedisch chirurg een MRI scan werd gemaakt. T2 relaxatietijden namen statistisch significant toe met hogere leeftijd en hoger BMI. Bij patiënten met verwachte mediale kraakbeenschade waren de mediale T2 waarden van het femur significant hoger dan de laterale, terwijl bij patiënten met verwachte laterale kraakbeenschade de laterale T2 waarden van de tibia significant hoger waren. Knieklachten die ontstonden als gevolg van een trauma vertoonden een acute verhoging van de T2 waarden. Er werd geen relatie gevonden met klinische symptomen. Onze studie toonde aan dat T2 relaxatietijden afhankelijk zijn van leeftijd, BMI en het type letsel. Deze resultaten benadrukken dat het erkennen van deze variaties van groot belang is bij het uitvoeren van T2 mapping in een klinische populatie.

Een andere overweging is dat studies naar de effecten van artrosebehandelingen grote groepen deelnemers vereisen en daardoor vaak in multicenter verband moeten plaatsvinden. Bij het toepassen van kwantitatieve beeldvorming in een multicenter studie is een belangrijk aspect de verscheidenheid aan MRI-scannerfabrikanten en scannermodellen die op de markt zijn. In het geval van MRI hebben factoren zoals veldsterkte, spoeltype en scanparameters invloed op de kwantitatieve uitkomsten. Zonder kennis van deze invloeden kunnen kwantitatieve beeldvormende technieken niet worden toegepast in multicenter studies. Het doel van de studie beschreven in **hoofdstuk 5** was om de reproduceerbaarheid over tijd, oftewel de longitudinale reproduceerbaarheid, en multicenter variatie van T2 mapping van kniekraakbeen te bepalen. Bij vier gezonde proefpersonen werd tweemaal een T2 mapping scan van de knie gemaakt in vijf verschillende centra met een interval van zes maanden. Daarnaast werd ook een model dat de menselijke kraakbeen T2 waarden nabootst, oftewel een fantoom, gescand in elk centrum. De centra hadden verschillende MRI scanners met verschillende veldsterkten en T2 mapping scanprotocollen. We vonden goede tot uitstekende longitudinale reproduceerbaarheid van de T2 waarden van de verschillende kraakbeenregio's. Er waren duidelijke verschillen in T2 waarden tussen de verschillende centra. Deze verschillen waren echter wel consistent tussen de centra zowel bij de proefpersonen als bij het fantoom. Kortom, de resultaten van deze studie suggereren dat T2 mapping kan worden gebruikt om kraakbeendegeneratie longitudinaal te beoordelen in multicenterstudies. Aangezien T2 waarden per centrum verschillen moeten de absolute T2 waarden van multicenter studies, waarbij verschillende apparatuur wordt gebruikt, niet worden samengevoegd.

Bij het gebruik van kwantitatieve MRI om artrosebehandelingen te evalueren kan de behandeling zelf invloed hebben op de kwantitatieve uitkomsten. Bijvoorbeeld bij HTO rijst de vraag in hoeverre de metingen worden beïnvloed door de aanwezigheid van de

metalen implantaten. In **hoofdstuk 6** hebben we onderzocht wat de invloed is van twee veelgebruikte HTO fixatiemethoden op de uitkomsten van T2 mapping. Hiervoor werden 11 menselijke kadaverknieën gescand voor en na het inbrengen van een titanium plaat en schroeven of kobaltchroom krammen. De kobaltchroom krammen veroorzaakten artefacten in het magnetische veld die het onmogelijk maakten om het kniekraakbeen te segmenteren, en dus T2 relaxatietijden te berekenen, in de laterale kraakbeenregio's van de knie. In de knieën waarin titanium materiaal was gebruikt waren er geen significante verschillen in T2 relaxatietijden tussen de twee scans. Dit gold ook voor de kraakbeenregio's die niet werden beïnvloed door de artefacten van de kobaltchroom krammen. Onze resultaten suggereren dat nauwkeurige T2 mapping na een HTO procedure mogelijk is in alle kraakbeengebieden bij gebruik van titanium fixatiemateriaal en in de meeste gebieden bij gebruik van kobaltchroom krammen.

De laatste overweging heeft te maken met de verscheidenheid aan kwantitatieve MRI technieken die beschikbaar zijn voor het beoordelen van de kraakbeenkwaliteit. Het combineren van technieken die verschillende aspecten van de kraakbeensamenstelling meten biedt een meer omvangrijke beoordeling van de artrosestatus. Sommige technieken vereisen het gebruik van een contrastmiddel, terwijl dat voor andere niet nodig is. Wanneer deze technieken worden gecombineerd, betekent dit doorgaans dat ze in afzonderlijke scansessies worden uitgevoerd. Deze aanpak is tijdrovend en niet gebruiksvriendelijk. Een ideale situatie zou zijn om deze verschillende technieken binnen één sessie te kunnen combineren. In **hoofdstuk 7** hebben we onderzocht of het mogelijk is kniekraakbeen te beoordelen met T2 mapping en 'delayed gadolinium enhanced MRI of cartilage' (dGEMRIC) in één scansessie na toediening van contrastmiddel. In deze studie werd T2 mapping uitgevoerd bij 10 gezonde vrijwilligers na verschillende activiteiten die horen bij het dGEMRIC protocol, i.e. 10 minuten fietsen en 90 minuten wachten, en bij 16 patiënten met knieartrose voor en na intraveneuze toediening van een dubbele dosis gadolinium-dimeglumine-contrastmiddel. Er werden enkele kleine verschillen tussen de scans gevonden die, op één meting na, kleiner waren dan het kleinste verschil dat kan worden onderscheiden van meetfouten (smallest detectable change (SDC)). De verschillen waren bovendien niet consistent. Onze resultaten suggereren dat T2 mapping en dGEMRIC betrouwbaar gecombineerd kunnen worden in één scansessie om de samenstelling van kraakbeen bij knieartrose te beoordelen.

Hoofdstuk 8 is een algemene bespreking van het onderzoek dat in dit proefschrift wordt gepresenteerd, inclusief de beperkingen en aanbevelingen voor verder onderzoek.

Conclusie

Het onderzoek dat in dit proefschrift wordt beschreven draagt bij aan het nemen van weloverwogen beslissingen met betrekking tot het toepassen van valgiserende therapie bij patiënten met mediale knieartrose. Daarnaast behandelt het overwegingen die essentieel zijn voor de succesvolle toepassing van kwantitatieve beeldvormende technieken voor de vroegtijdige detectie van artrose en de evaluatie van interventiestudies voor artrose. De belangrijkste bevindingen kunnen als volgt worden samengevat:

- Op groepsniveau is een HTO effectiever in het verminderen van kniepijn dan een valgiserende kniebrace bij patiënten met mediale knieartrose.
- Zowel T2 mapping als kwantitatieve SPECT-CT zijn in staat om binnen één jaar veranderingen in kraakbeen en subchondraal bot te detecteren door valgiserende therapie. Beide technieken belichten het artroseproces op een verschillende manier en zijn daarom waardevol en complementair bij het monitoren van artrosetherapieën.
- T2 relaxatietijden zijn afhankelijk van leeftijd, BMI en het type letsel. De invloed van deze factoren moet meegenomen worden bij het gebruik van T2 mapping in een klinische populatie.
- T2 mapping kan worden gebruikt voor longitudinale beoordeling van kraakbeendegeneratie in multicenterstudies. Echter, gezien de verschillen in absolute T2 waarden tussen centra met verschillende MRI apparatuur, dienen de T2 waarden niet te worden samengevoegd.
- Nauwkeurige T2 mapping na een HTO procedure is mogelijk zolang er geen visuele vervorming van het kraakbeen is als gevolg van artefacten door het ingebrachte materiaal.
- T2 mapping en dGEMRIC kunnen betrouwbaar worden uitgevoerd in één scansessie om de biochemische samenstelling van het kraakbeen bij knieartrose te beoordelen.

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List of abbreviations

3D	Three dimensional
95% CI	95% confidence interval
99m Tc-HDP	Technetium-99m Hydroxymethylene diphosphonate
ADL	Activities of Daily Living
ANOVA	Analysis of Variance
AP	Anteroposterior
β	Standardized Coefficients
Bq/ml	Becquerel per milliliter
BMI	Body Mass Index
CI	Confidence Interval
CI-95	95% confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CT	Computed Tomography
CV	Coefficient of Variation
cwHTO	Closing Wedge High Tibial Osteotomy
DCE-MRI	Dynamic Contrast-Enhanced Magnetic Resonance Imaging
DESS	Double Echo Steady State
dGEMRIC	Gelayed Gadolinium Enhanced Magnetic Resonance Imaging of Cartilage
DMOADs	Disease-Modifying Osteoarthritis Drugs
EMA	European Medicines Agency
FDA	United States Food and Drug Administration
Fem_post	Posterior Femoral Condyle
Fem_wb	Weight-bearing Femoral Condyle
FOV	Field of View
FS	Fat Suppression
FSPGR	Fast Spoiled Gradient-Echo
FSE	Fast Spin Echo
FU	Follow-up
GAG	Glycosaminoglycan
gagCEST	Glycosaminoglycan Chemical Exchange Saturation Transfer
Gd-DTPA2-	Gadolinium Dimeglumine

GDPR	General Data Protection Regulation
HKA	Hip-Knee-Ankle
HSS	Hospital for Special Surgery Knee Rating Scale
HTO	High Tibial Osteotomy
Hz	Hertz
ICC	Intraclass Correlation Coefficient
ICOAP	Intermittent and Constant Osteoarthritis Pain score
i.e.	Id Est (that is)
KOOS	Knee Injury and Osteoarthritis Outcome Score
K&L	Kellgren & Lawrence (grading of knee OA)
Kg	Kilogram
Kg/m^2	Kilograms per square meter
M^2	Square meter
MC	Medical Center
MCID	Minimal Clinically Important Difference
MDC	Minimal Detectable Change
MEC	Medisch Ethische Toetsingscommissie (Institutional Review Board)
mg/mLq	Milligram per Milliliter
min	Minutes
mm	Millimeter
mmol	Millimole
MRI	Magnetic Resonance Imaging
ms	Milliseconds
n	Number
Na	Not Applicable
NRS	Numeric Rating Scale
NSAID	Non-Steroidal Anti-Inflammatory Drugs
NTR	National Trial Register
OA	Osteoarthritis
OAI	Osteoarthritis Initiative
OARSI	Osteoarthritis Research Society International
owHTO	Opening Wedge High Tibial Osteotomy
p	Probability

PE	Phase Encoding
PET	Positron Emission Tomography
Plat_wb	Weight-bearing Tibial Plateau
PROMs	Patient-Reported Outcome Measures
QIBA	Quantitative Imaging Biomarker Alliance
qMRI	Quantitative Magnetic Resonance Imaging
QoL	Quality of Life
R	Receive
R^2	coefficient of determination
REML	Restricted Maximum Likelihood
RCT	Randomized Controlled Trial
RO	Readout
ROI	Region of Interest
RMS-CV	Root-Mean-Square Coefficient of Variation
RSNA	Radiological Society of North America
SD	Standard Deviation
SDC	Smallest Detectable Change
SE	Spin Echo
S&R	Send and Receive
SPECT	Single Photon Emission Computed Tomography
SPECT-CT	Single Photon Emission Computed Tomography - Computed Tomography
SUV	Standard Uptake Value
SUVmax	Maximum Standard Uptake Value
T	Tesla (unit of magnetic flux density)
T1rho	Spin-Lattice Relaxation Time Constant in Rotating Frame
T2	Transverse Relaxation Time
TE	Echo Time
Tib_wb	Weight-bearing Tibial Plateau
TKA	Total Knee Arthroplasty
TR	Repetition Time
UKA	Unicompartmental Knee Arthroplasty
WHO	World Health Organization

PhD portfolio

Personal Details	
PhD student	Joost Verschueren
Department	Department of Orthopaedics and Sports Medicine and Department of Radiology & Nuclear Medicine, Erasmus MC University Medical Center Rotterdam, The Netherlands
PhD period	2013 - 2024
Doctoral supervisor	S.M.A Bierma-Zeinstra, PhD E.H.G. Oei, MD, PhD
Daily advisor	M. Reijman, PhD

Courses: General	**Year**	**ECTS**
Good Clinical Practice (Erasmus MC)	2014	1
Systematic Literature Retrieval 1 & 2 (Erasmus MC)	2014	0.5
Research Integrity (Erasmus MC)	2015	0.3
3rd Osteotomy congress, Luxembourg, Luxembourg	2015	0.5
Biomedical Writing and Communication (Erasmus MC)	2016	3
Osteotomy course (UMC Utrecht)	2023	0.5
Courses: Statistics (NIHES)	**Year**	**ECTS**
Introduction to Data-analysis	2014	2
Clinical Trials	2015	2
Missing values in Clinical Research	2017	2
Repeated Measurements	2017	2
Courses: Imaging	**Year**	**ECTS**
MRI Safety and Scanning (Erasmus MC)	2013	2
Radiation Protection Course 5R (Erasmus MC)	2015	0.5
Basic Course in Applied MR Techniques (ESMRMB)	2016	1.5
Radiation hygiene for Medical Specialist (LUMC)	2020	2
(Inter)national Podium Presentations	**Year**	**ECTS**
Brace versus osteotomy for medial knee osteoarthritis: study design, imaging technique and obstacles. *Nordic Meeting on Quantitative Imaging of Cartilage, Kuopio, Finland*	2014	1
T2 relaxation times of arthritic knee cartilage unaffected by gadolinium contrast agent. *Radiological Society of the Netherlands Annual Meeting, Den Bosch, The Netherlands*	2014	1
T2 relaxation times of knee articular cartilage in osteoarthritis patients are not influenced by gadolinium contrast agent. *RSNA Annual Meeting, Chicago, USA*	2014	1
Influence of exercise and waiting time required for dGEMRIC on T2 relaxation times of knee cartilage at 3T *ISMRM IWOAI, Pacific Grove, USA*	2015	1

Influence of exercise and waiting time required for dGEMRIC on T2 relaxation times of knee cartilage at 3T *Nordic Meeting on Quantitative Imaging of Cartilage, Utrecht, The Netherlands*	2015	1
Challenges of Implementing Quantitative MRI Techniques in Clinical Studies on High Tibial Osteotomies: A Human Cadaver Study on the Feasibility of T2 Mapping Near Metal *Dutch Orthopaedic Association Spring Meeting, Utrecht, The Netherlands, 20-05-2016.*	2016	1
Quantification of osteoarthritis using SPECT/CT and MRI *EANM YIM, Vienna, Austria*	2016	1
Update on the Brace versus Osteotomy Study *Dutch Orthopaedic Association Autumn Meeting, Veldhoven, The Netherlands*	2016	1
Quantification of osteoarthritis using SPECT/CT and MRI *Nordic Meeting on Quantitative Imaging of Cartilage, Bastad, Sweden (presented by EHG Oei)*	2017	0.3
Quantitative subchondral bone perfusion imaging in knee osteoarthritis using DCE-MRI *Nordic Meeting on Quantitative Imaging of Cartilage, Bastad, Sweden (presented by BA de Vries)*	2017	0.3
(Inter)national Poster Presentations	**Year**	**ECTS**
Challenges for implementation of T2-mapping in a large clinical trial of high tibial osteotomy: A human cadaver study to assess the feasibility of T2-mapping MRI near metal *ISMRM IWOAI, Pacific Grove, USA*	2015	0.5
Titanium fixation devices do not influence T2 relaxation times of knee articular cartilage after high tibial osteotomy: a human cadaver study *RSNA Annual Meeting, Chicago, USA*	2015	0.5
Influence of dGEMRIC protocol on T2 relaxation times of knee cartilage in healthy volunteers and osteoarthritis patients *OARSI World Congress, Amsterdam, The Netherlands*	2016	0.5
Cartilage T2 Relaxation Times: Reproducibility In A Multicenter Trial *IWOAI, Oulu, Finland*	2016	0.5
Challenges of Quantitative Magnetic Resonance Imaging after High Tibial Osteotomy: A Human Cadaver Study to Assess the Feasibility of T2-mapping near Titanium *ISAKOS, Shanghai, China*	2017	0.5
Teaching		
Teaching medical master students statistics and biomedical reading and writing skills for their orthopedic research internship	2014-2017	2
Teaching medical students attending the minor 'Sports medicine and traumatology' biomedical reading and physical examination	2014-2017	1
Teaching nurses about high tibial osteotomy at the Erasmus MC and Elisabeth-TweeSteden Hospital	2015, 2021	1

Supervising the master thesis of Melek Ikinci: 'Dynamic Contrast Enhanced Magnetic Resonance Imaging of subchondral bone in patients with knee osteoarthritis'	2016	4
Supervising the master thesis of Stephan van Langeveld: 'Correlation of quantitative MRI technique T2-mapping and clinical symptoms of OA'	2017	4
Total Workload in ECTS		**43**
Grants		
Conference Travel Grant *Erasmus Trustfonds*	2015	
Trainee Stipend *International Society for Magnetic Resonance in Medicine (ISMRM)*	2015	
Young Investigators Meeting Travel Grant *European Association of Nuclear Medicine (EANM)*	2016	
Travelling Fellowship on osteotomies around the knee, visiting professor Matthieu Ollivier (Aix-Marseille University Hospital, Marseille, France) and professor Wolf Petersen (Martin Luther Krankenhaus, Berlin, Germany) *Vereniging Orthopaedisch Chirurgische Assistenten (VOCA)*	2023	
Peer Reviewer		
Osteoarthritis and Cartilage, Cartilage, European Radiology and Quantitative Imaging in Medicine and Surgery	2014-2017	

ECTS (European Credit Transfer and Accumulation System) credits is a standardized measure for workload in higher education across the European Union. One ECTS credit comprises 28 hours.

List of publications

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Curriculum vitae

Joost Verschueren was born on November 26, 1985 in Enschede, The Netherlands. After graduating from the Stedelijk Lyceum Kottenpark in 2004, he took a gap year to travel to Australia and Asia. During his high school years, he was torn between studying mechanical engineering and medicine. Eventually, he chose medicine at the Radboud University in Nijmegen. However, his keen interest in technology quickly sparked a fascination with orthopedic surgery. His first exposure to orthopedic scientific research occurred as a medical student in the research group of Professor Wim Schreurs. This experience led to an orthopedic research internship at the Institute of Health and Biomedical Innovation of the Queensland University of Technology in Brisbane, Australia, in 2009. During the latter part of his medical training, Joost completed a clinical internship in tropical medicine in Sengerema, Tanzania, in 2012. Following the completion of his medical degree, he started working as a non-training resident in general surgery and orthopedic surgery at the BovenIJ Hospital in Amsterdam. Due to his desire to gain further scientific knowledge and skills in orthopedic surgery, he commenced a PhD track in late 2013 at the Departments of Orthopedic Surgery and Radiology at the Erasmus MC University Medical Center Rotterdam, which resulted in this thesis. In January 2018, he started his orthopedic surgery residency at the Maasstad Hospital Rotterdam, Erasmus MC and Elisabeth-TweeSteden Hospital in Tilburg. He will complete his training in the course of 2024. Joost resides in Rotterdam with his girlfriend Nicolein and their children Doris and Ted. In his leisure time, he enjoys playing (bass) guitar, wood working and cycling.