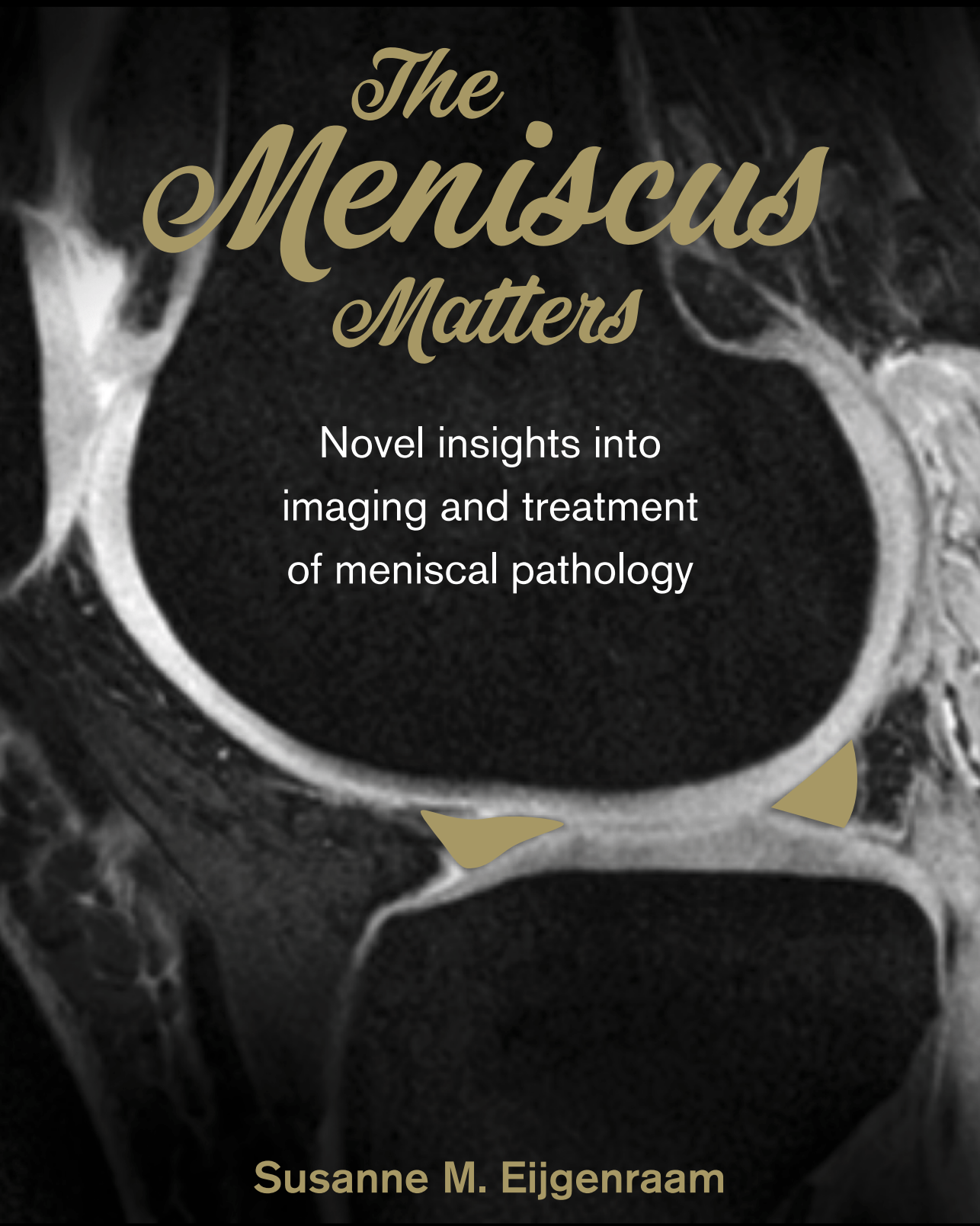

The Meniscus Matters

Novel insights into imaging and treatment of meniscal pathology

Susanne M. Eijgenraam

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The Meniscus Matters

Novel insights into imaging and treatment of meniscal pathology

Nieuwe inzichten in beeldvorming en behandeling van meniscus letsel

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
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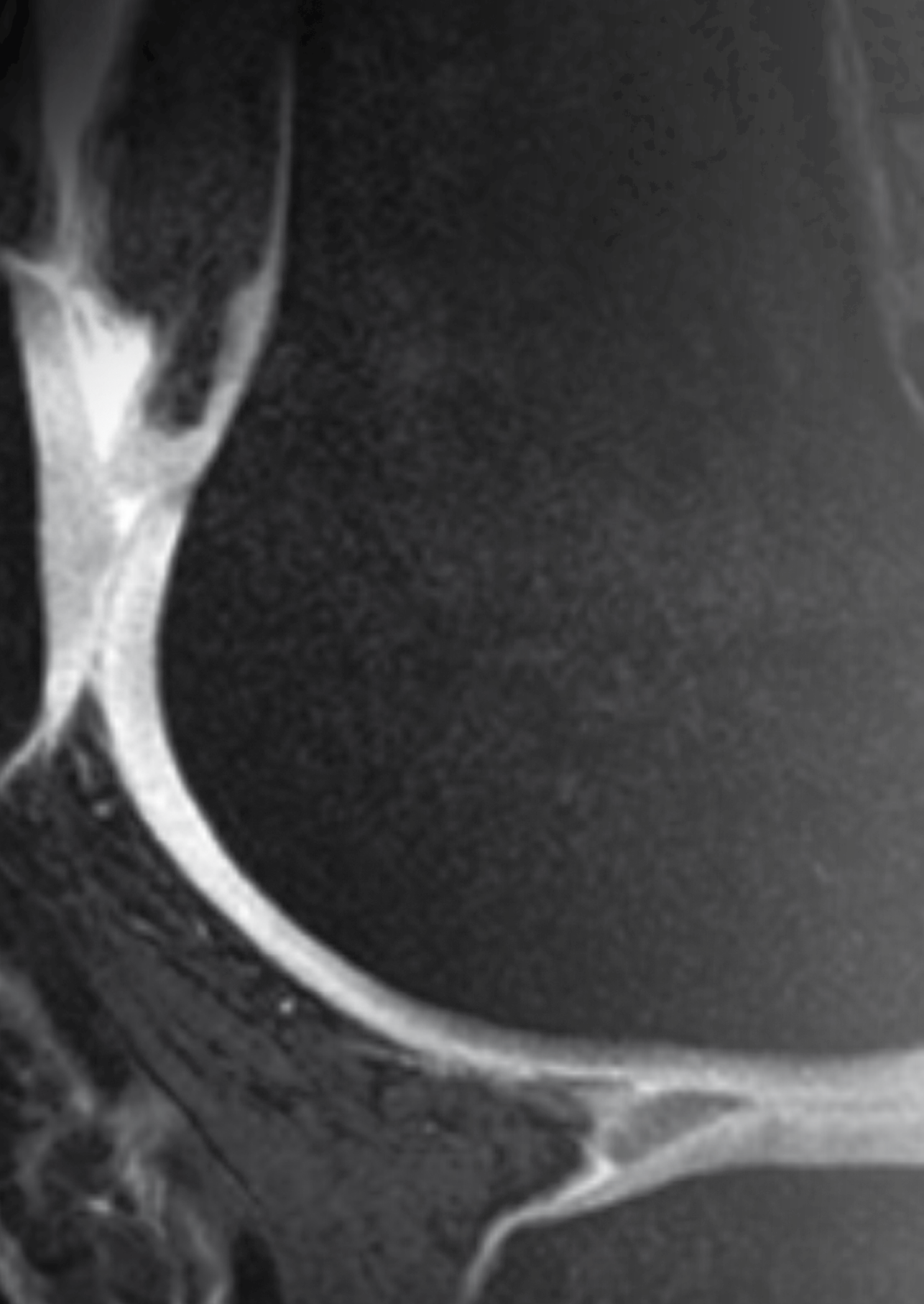
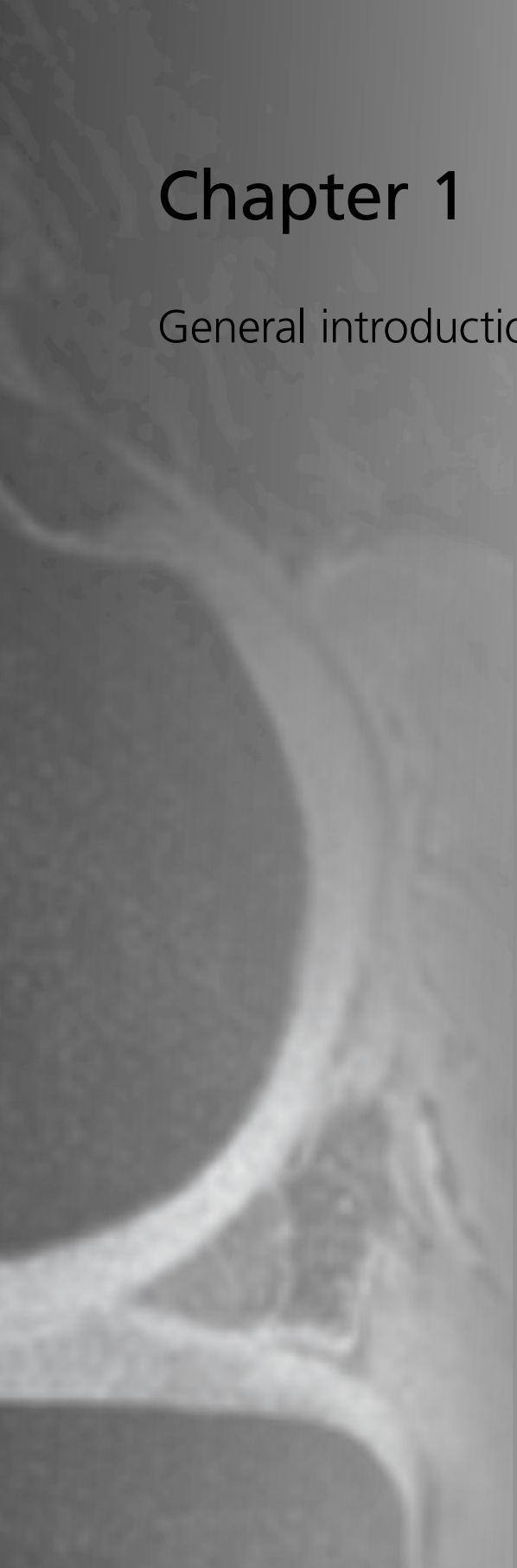


Chapter 1

General introduction



The more I learn, the more I realize how much I don't know
– Albert Einstein

Meniscal surgery has been a default treatment for meniscal tears for generations of clinicians and patients; it remains the most frequently performed orthopedic procedure worldwide. In recent years, however, advances in imaging as well as clinical and biomechanical studies have led to progressive insights into the meniscus' major biomechanical function. The more we have learned about the meniscus, the more questions have been raised regarding the etiology of meniscal pathology, the efficacy of current treatments, and the optimal imaging techniques.

The meniscus: anatomy and function

The menisci are two fibrocartilaginous structures interposed between the femoral condyles and the tibial plateau (Figure 1). The word ''meniscus" is derived from the Ancient Greek term for moon, mene, referring to its half-moon shape (Figure 2-A, 2-B). Each human knee contains two menisci: one in the medial (i.e., medial meniscus) and one in the lateral (i.e., lateral meniscus) joint compartment (Figure 2-A). Both menisci are wedge-shaped in cross section (Figure 2-C). The peripheral base of the medial meniscus is tightly attached to the joint capsule (Figure 2-C), whereas the attachment of the lateral meniscus is more mobile. A disruption in the attachment of the capsule to the lateral meniscus, the so-called popliteal hiatus, permits the popliteal tendon to pass through [1]. In addition, both menisci are attached to the tibial plateau via the anterior and posterior roots. The tibial attachments of the lateral meniscus are placed more centrally (in an anterior-posterior view) than the tibial attachments of the medial meniscus, resulting in the lateral meniscus being less fixed than the medial meniscus (Figure 2-A) [1-6].

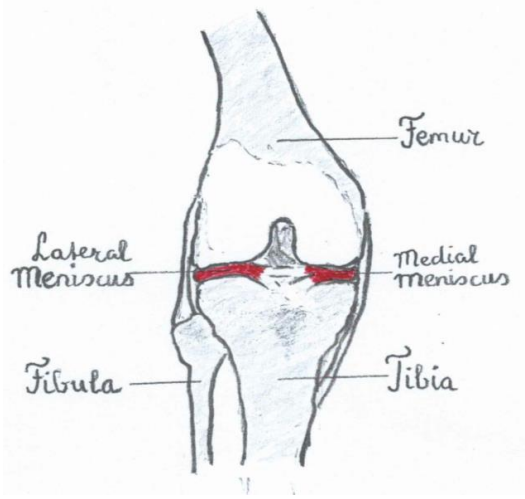


Figure 1. Anatomy of the human menisci. Right knee, frontal view, patella removed. Knee is slightly flexed. Medial and lateral menisci are highlighted in red. *Artwork by the author.*

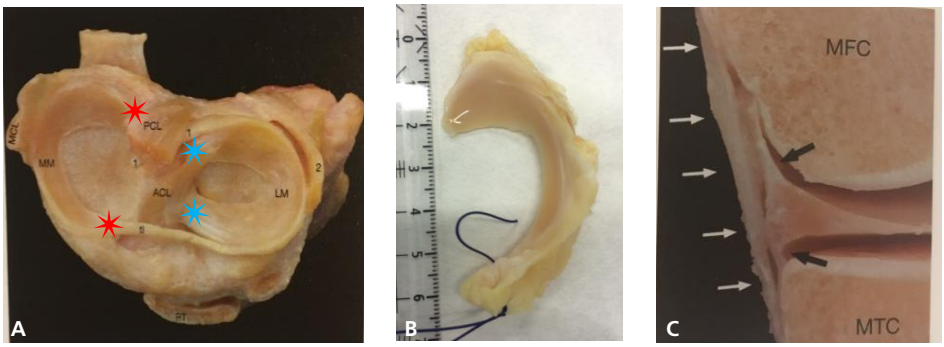


Figure 2. Attachments of the menisci. A) Left cadaveric knee joint, top view, femur removed. Note the difference in tibial attachments of meniscal roots between medial (red stars) and lateral (blue stars) meniscus. B) Medial meniscus, *ex vivo*, obtained during upper leg amputation in a 53-year-old male with no previous history of knee injury. C) Cross section of cadaveric medial knee compartment in coronal plane at the level of the medial collateral ligament (white arrows). Abbreviations: MM = medial meniscus; LM = lateral meniscus; ACL = anterior cruciate ligament; PCL = posterior cruciate ligament; PT = patellar tendon; MCL = medial collateral ligament; MFC = medial femoral condyle; MTC = medial tibial condyle. *Pictures 2-A and 2-C by dr. U. Zdanowicz, from Surgery of the Meniscus, Springer 2016; reproduced with permission.*

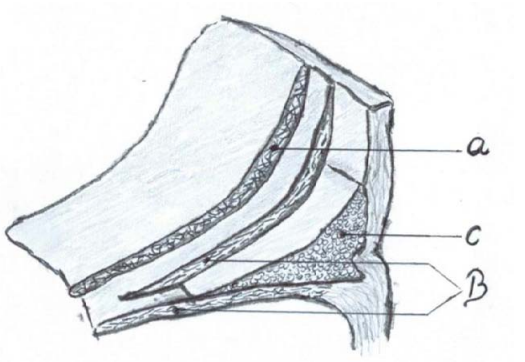


Figure 3. Cross-sectional view of the meniscus showing its collagen fiber configuration. A) Tightly woven superficial mesh layer. B) Radially oriented collagen fibers. C) Circumferentially oriented collagen fibers. *Artwork by the author.*

The meniscus contains 70% water and 30% organic matter. Collagen (mainly type 1) accounts for 75% of the dry mass [2,7,8]. Menisci consist of firmly woven collagen fibers, mostly arranged in a circumferential pattern. Some of the fiber bundles in the central zone and superficial layers are radially aligned (Figure 3). This specific pattern of fiber orientation provides strength and the ability to convert compression load into tensile stress [2,9-11]. The vascular supply is derived from branches of the inferior and superior geniculate arteries, infiltrating the peripheral zones of the menisci (often called the "red zone"). The central third

of the meniscus is avascular in adults (often called the "white zone") and receives nutrients by diffusion of synovial fluid [2,12,13].

Although described as ''irrelevant remains of leg muscle" in the past [14], it is now clear that the menisci have an important biomechanical function in the knee. Their primary function is shock absorption and load distribution across the tibiofemoral joint (Figure 4). The menisci transmit and distribute at least 50-70% of the total load when the knee is in extension and 85-90% when in flexion [15,16]. Moreover, they have a role in stabilization and fluid distribution within the knee joint [11,17-21].

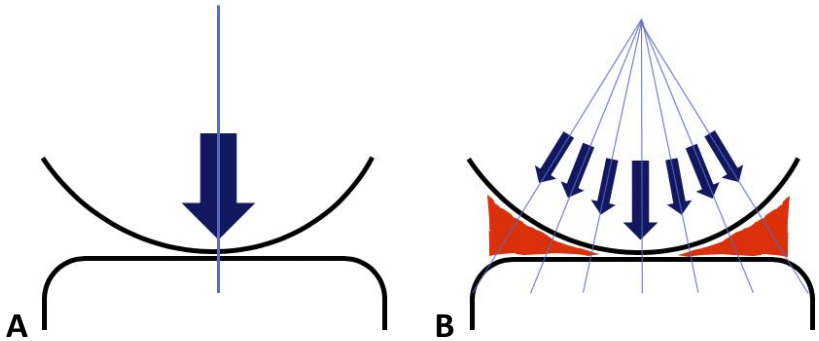


Figure 4. Biomechanical function of the meniscus. Schematic view of the knee joint in sagittal plane, in absence (A) and in presence (B) of the meniscus. The menisci, highlighted in red, distribute compressive load (blue arrows) and decrease contact stress force throughout the knee joint.

Meniscal pathology: incidence and etiology

With a general incidence of 60-70 per 100.000 individuals per year, a meniscal tear is among the most common types of knee injury [22-24]. Clinical presentation may include knee pain, mechanical symptoms (i.e., locking complaints) and, in many cases, significant disability, thereby creating a great burden for patient and society [24]. Meniscal tears are traditionally classified into two main categories: traumatic versus degenerative tears. This classification is mainly based on onset of complaints (i.e., traumatic or degenerative); however, the patient's age and other pathological findings in the knee (e.g., osteoarthritis and injury of other ligaments, such as anterior cruciate ligaments) play a role as well [1,17,24-27].

Traumatic meniscal tears have an acute onset, most often seen in young, active individuals and mostly as a result of twisting injuries. This often occurs during sports activities (soccer and field hockey are high-risk sports); however, traumatic meniscal tears resulting from minor accidents in daily life are also common. Combined traumatic injuries of the (mostly lateral) meniscus and anterior cruciate ligament are frequently observed [28,29]. Traumatic tears are often oriented in the longitudinal or oblique direction, running parallel to the circumferentially arranged collagen fibers, although various other tear patterns are possible as well [1,30-32]. Traumatic meniscal tears can be subdivided into 1) obstructive and 2) non-obstructive tears.

An obstructive tear is when the torn part of the meniscus is (partly) dislocated, resulting in ''locking" of the knee. The remaining cases are non-obstructive tears [33].

In contrast to traumatic tears, *degenerative meniscal tears* develop gradually. These tears are often seen in the middle-aged or the elderly, as a result of repetitive normal forces acting upon a meniscus with already ongoing degenerative tissue changes [1,26]. Degenerative tears are typically horizontal cleavage lesions and is often associated with pre-existing cartilage degeneration [25,34]. Increasing evidence suggests that a symptomatic degenerative meniscal tear is not an isolated entity but a sign of knee osteoarthritis (OA) [1,18,35]; however, this does not necessarily mean that pain symptoms in a patient with a degenerative tear in an osteoarthritic knee are caused by the meniscal damage. The prevalence of degenerative meniscal tears, as detected on magnetic resonance imaging (MRI) in the general population above 70 years old, is about 45% [36]. Remarkably, 60% of these degenerative tears on MRI are asymptomatic [36] and, therefore, can be considered incidental findings on knee MRI. The biological mechanism leading to degenerative meniscal tears and the complex role of the meniscus in the pathological process in knee OA are still largely unknown.

(MR) Imaging of meniscal pathology

Since its introduction in the 1980s, conventional MRI has been the gold standard for meniscus imaging in clinical practice and research [1]. A great advantage of MRI is that multiple relevant knee structures, such as menisci, cartilage, and synovium, can be assessed within one examination [37]. For detecting meniscal tears, in general, spin echo based proton-density (PD) weighted sequences with an echo time around 35 ms and long repetition time, in the sagittal and coronal plane, are considered most appropriate (Figure 5-A)[38]. If performed correctly, MRI can detect a meniscal tear accurately in > 90% of the cases [26,39-41].

Meniscal damage on MRI may comprise the following: 1) tissue degeneration (intra-substance alterations, measured by increased signal intensity or T_2 relaxation times); 2) meniscal extrusion (i.e., radial displacement of the meniscus); and 3) morphological damage, that is, meniscal tears or maceration[42-45]. A meniscal tear is usually characterized by a linear intrameniscal signal communicating with the meniscal surface. Maceration means a completely worn-down meniscus, defined as loss of morphological substance of the meniscus on MRI [46].

In a clinical setting, radiologists usually describe meniscal tears in free text. In clinical research, on the other hand, a more standardized approach, in terms of reproducibility, is needed. Several semiquantitative MRI classification systems for the knee, such as the MRI Osteoarthritis Knee Score (MOAKS) [46], have been developed for this purpose. In these classification systems, MRI findings of multiple knee structures, including cartilage and menisci, are scored.

Although sensitive to alterations of meniscal morphology, conventional MRI has limited capability to detect early changes in the meniscus before gross morphological abnormalities occur. This hampers early therapeutic interventions and disease monitoring. To overcome

this limitation, quantitative MRI (qMRI) techniques (sometimes referred to as compositional or molecular MRI techniques), such as T_2 mapping (Figure 5-B), T_1rho, and ultra-short echo time T_2* mapping (UTE-T2*), have been developed [47-54]. By quantitatively assessing key biochemical meniscus components – collagen and proteoglycans –, qMRI techniques allow the detection of early stages of meniscal degeneration and accurate follow-up [47,55-57]. Moreover, they allow a refined grading of meniscus pathology, increasing the discriminative power to distinguish degrees of meniscus degeneration [47,57]. Among qMRI techniques, T_2 mapping is the most widely used in the field of musculoskeletal research [37,58,59].

The main advantage of T_2 mapping is that its implementation is relatively easy, as (contrary to most other qMRI techniques) no contrast or special MR hardware is required. What exactly is measured with T_2 mapping remains controversial, yet most researchers agree that increased T_2 relaxation times indicate an increased mobility of water protons as a result of damage to the collagen matrix of the meniscus. Matrix degradation may reflect tissue degeneration, thus providing an indirect measure for biochemical composition [54,57,60-62].

Before qMRI techniques, such as T_2 mapping, can find their way to clinical practice, thorough assessment of its accuracy (i.e., do we measure what we want to measure?), reliability (i.e., are measurements reproducible?) and feasibility (e.g., what are the technical requirements? And is the acquisition time acceptable?).

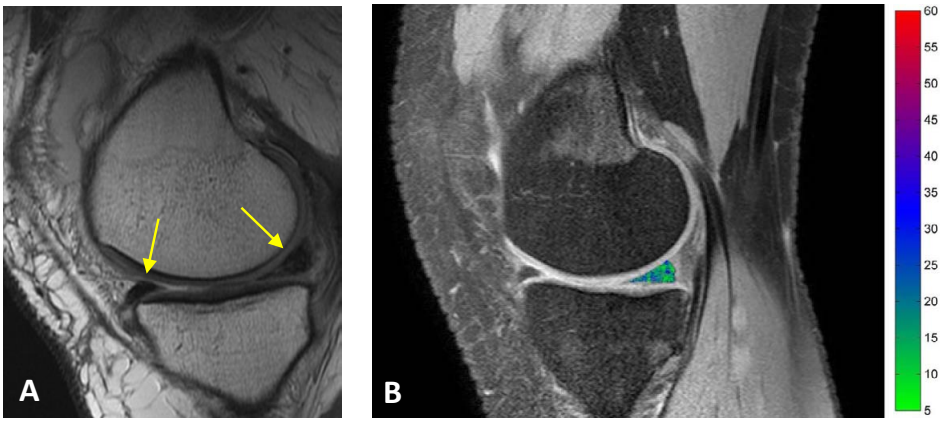


Figure 5. MR Imaging of the meniscus. A) Sagittal Proton-Density weighted image, medial compartment, anterior and posterior meniscal horns (yellow arrows) depicted as black triangles. B) Sagittal T_2 mapping image with colourmap of the posterior horn of the lateral meniscus.

Treatment of meniscal pathology

Treatment options for meniscal tears comprise non-operative and operative approaches. The choice of treatment strategy (i.e., non-operative or operative) depends upon the onset of complaints (i.e., traumatic or degenerative), the nature and extent of complaints, type and location of the meniscal tear, the presence of significant mechanical symptoms (i.e.,

locked knee), and the presence of additional knee pathology [33,63,64]. Non-operative treatment comprises pain medication, relative rest and exercise therapy. The main goals of exercise therapy for meniscal tears are to reduce hydrops, to optimize range of motion, to increase muscle coordination and strength, and to restore knee function [65]. Operative options to treat meniscal tears include arthroscopic partial meniscectomy (APM) or, in some cases, meniscal repair [1,66,67]. APM means removing the torn part of the meniscus; repair means suturing the tear. Whether a meniscal tear is suitable for repair depends on the type of tear, tear length, and location of the tear, assessed on MRI [68-70]. Longitudinal tears in the vascularized portion (i.e., the "red zone") of the meniscus have the highest chance of success in the context of meniscal repair [1,69]. The growing awareness of the major biomechanical function within the knee joint has led to an increasing interest in meniscal repair, yet only about 5% of meniscal tears are sutured [68].

For the treatment of *degenerative tears,* the European Society of Sports Traumatology, Knee Surgery and Arthroscopy (ESSKA) reached a consensus in 2016, based on clinical studies. The ESSKA recommends starting with non-operative treatment for at least 3 months, ''except in the case of considerable mechanical symptoms". If this approach fails, and no signs of OA are seen on radiograph or MRI, arthroscopic partial meniscectomy may be indicated [63].

Regarding *traumatic meniscal tears*, there is little consensus on treatment strategy. According to the guideline ''arthroscopy of the knee" of the Dutch Orthopedic Society, a traumatic tear in a "fixed locked knee" is an indication for arthroscopy within two weeks [64]. For all remaining cases, no recommendation can be given as no sufficient evidence is available. In most cases, an APM or repair is chosen, despite of the fact that no evidence is available regarding operative versus non-operative therapy for traumatic tears. To fill this gap, in Erasmus MC University Medical Center, we designed a randomized controlled trial (RCT) to compare APM with non-operative treatment in patients with traumatic tears: the STARR trial.

AIMS AND OUTLINE OF THIS THESIS

The STARR trial

The *STARR trial* is a multicenter open-labeled RCT, with eight participating hospitals (e.g. Máxima MC Eindhoven and Haaglanden MC Leidschendam), funded by the Dutch government, comparing APM (resection, not repair) with standardized exercise therapy. In total, 100 patients under 45 years without knee OA are included, with selection based on a solitary meniscal tear and acute onset, without a ''fixed locked knee". Locking complaints, in general, are not an exclusion criterium. Patients are followed for two years to investigate the differences between APM and exercise therapy with regard to 1) clinical effects (pain and function of the knee), 2) early cartilage degeneration using T_2 mapping MRI, and 3) cost-effectiveness. MRI with T_2 mapping is acquired in STARR patients at baseline and after

two years follow-up to assess early cartilage degeneration, as indicator for early-stage knee OA. Although the inclusion of patients already has finished, the follow-up of the STARR trial is currently still ongoing. The outcomes of the STARR trial will be available at the end of 2020; therefore, the results are not included in this thesis.

In the context of the STARR trial, several gaps in knowledge and research questions were identified concerning various aspects of meniscal pathology. The drive to answer those questions and to improve patient care was the basis of a number of research projects, the results of which are described in this thesis. This thesis is divided into two main themes: I) MR imaging and II) etiology and treatment of meniscal pathology.

PART I: MR IMAGING OF MENISCAL PATHOLOGY

How accurate is in vivo T_2 mapping to assess meniscal degeneration?

T_2 mapping, a quantitative MR imaging technique associated with tissue matrix degradation, is used in the *STARR trial* to measure cartilage degeneration after two years follow-up. Cartilage T_2 mapping has been widely studied and has been shown to be associated with cartilage degeneration [61,71]. Meniscal T_2 mapping is relatively new [47,57]. In order to use T_2 mapping as an imaging biomarker for meniscal degeneration in research and, eventually, in clinical practice, establishing its validity is essential. Validity of a technique means: does it measure what it is supposed to measure? Validation studies for meniscal T_2 mapping are limited; moreover, studies assessing in vivo meniscal T_2 mapping compared to histology have not yet been performed. Therefore, in this study, meniscal in vivo T_2 mapping was validated against the histological degree of degeneration, using meniscal tissue from patients with knee OA. The results are described in **Chapter 2**.

What is the reproducibility of T_2 mapping in a multicenter setting, such as the STARR trial?

The *STARR trial* is a multicenter study in which eight hospitals with, in total, 13 locations participate. In each of these hospitals, a ''STARR MRI protocol" (comprising routine clinical knee sequences and T_2 mapping) was implemented. To interpret T_2 mapping data from all these hospitals, information on multicenter comparability and longitudinal reproducibility is essential. Therefore, we performed a prospective pilot study to assess longitudinal reproducibility of cartilage T_2 mapping in a multicenter setting. The results of this study are described in **Chapter 3** and will be important for the analysis and interpretation of the results from the STARR trial in which T_2 values are an outcome measure as an indicator for early OA.

How can efficiency in MRI acquisition be improved?

T_2 mapping and other qMRI techniques are promising tools to non-invasively assess joint health, yet efficient acquisition is challenging. Current MRI protocols for the knee, including routine clinical sequences and a T_2 mapping sequence, are time consuming: they take 30-45 minutes [57,72]. Recently, the quantitative double-echo steady-state (qDESS) sequence was developed to increase acquisition efficiency. qDESS provides quantitative measures of cartilage and meniscus and diagnostic image quality in a single MRI scan with a scan time of only five minutes. qDESS comprises two echoes, and the combined signal of the two echoes can generate T_2 values. The sagittal qDESS images can be reformatted into coronal and axial reconstructions, thus, creating a 3D view of the knee. In collaboration with the Joint and Osteoarthritis Imaging with Novel Techniques (JOINT) lab of the Department at Radiology of Stanford University, we validated this relatively new and interesting sequence in OA patients. The results of this qDESS validation study are described in **Chapter 4**.

PART II: ETIOLOGY AND TREATMENT OF MENISCAL PATHOLOGY

The role of meniscal pathology in knee OA: cause or consequence?

As described earlier, the complex role of the meniscus in the development of knee OA is largely unknown. An important question in the etiology and disease development of knee OA concerns cartilage versus meniscus degeneration: what comes first in OA? To explore the temporal sequence of events in knee OA, a histology-based study in a mouse model for OA was performed as described in **Chapter 5**.

Is the classification "traumatic" versus "degenerative" meniscal tears as straightforward as assumed?

Or is it more like a continuum: are traumatically torn menisci already more or less degenerative? The complex role of meniscal tissue composition in the etiology of meniscal tears and the subsequent development of knee OA is not entirely clear. To test the "continuum hypothesis", we performed a cross-sectional histology-based observational study comprising different types of meniscal tissue. The results of this study are described in **Chapter 6**.

Clinical decision making in meniscal pathology: Should a traumatic meniscal tear be resected? - The STARR trial

The design of the STARR trial, a multicenter RCT in which APM is compared to conservative treatment in patients with traumatic meniscal tears, can be found in **Chapter 7**.

Clinical decision making in meniscal pathology: What are prognostic factors for outcome after APM?

It seems that there is a shift occurring regarding the treatment of meniscal tears: from "APM as standard of care" towards a more evidence-based approach of clinical decision making. Besides large clinical trials such as the STARR trial, evidence-based medicine also comprises an ''evidence-based patient selection" for APM. The identification of a subpopulation of patients with meniscal pathology who would likely benefit the most from APM requires knowledge of prognostic factors for the outcome after APM. To gain more insight into these prognostic factors, we performed a systematic literature review, as described in **Chapter 8**.

In **Chapter 9**, a general discussion regarding the study results in this thesis is provided. Clinical relevance, implications for research and clinical practice, future perspectives, and recommendations for further research are described. **Chapter 10** comprises a general summary of the studies and study results in this thesis.

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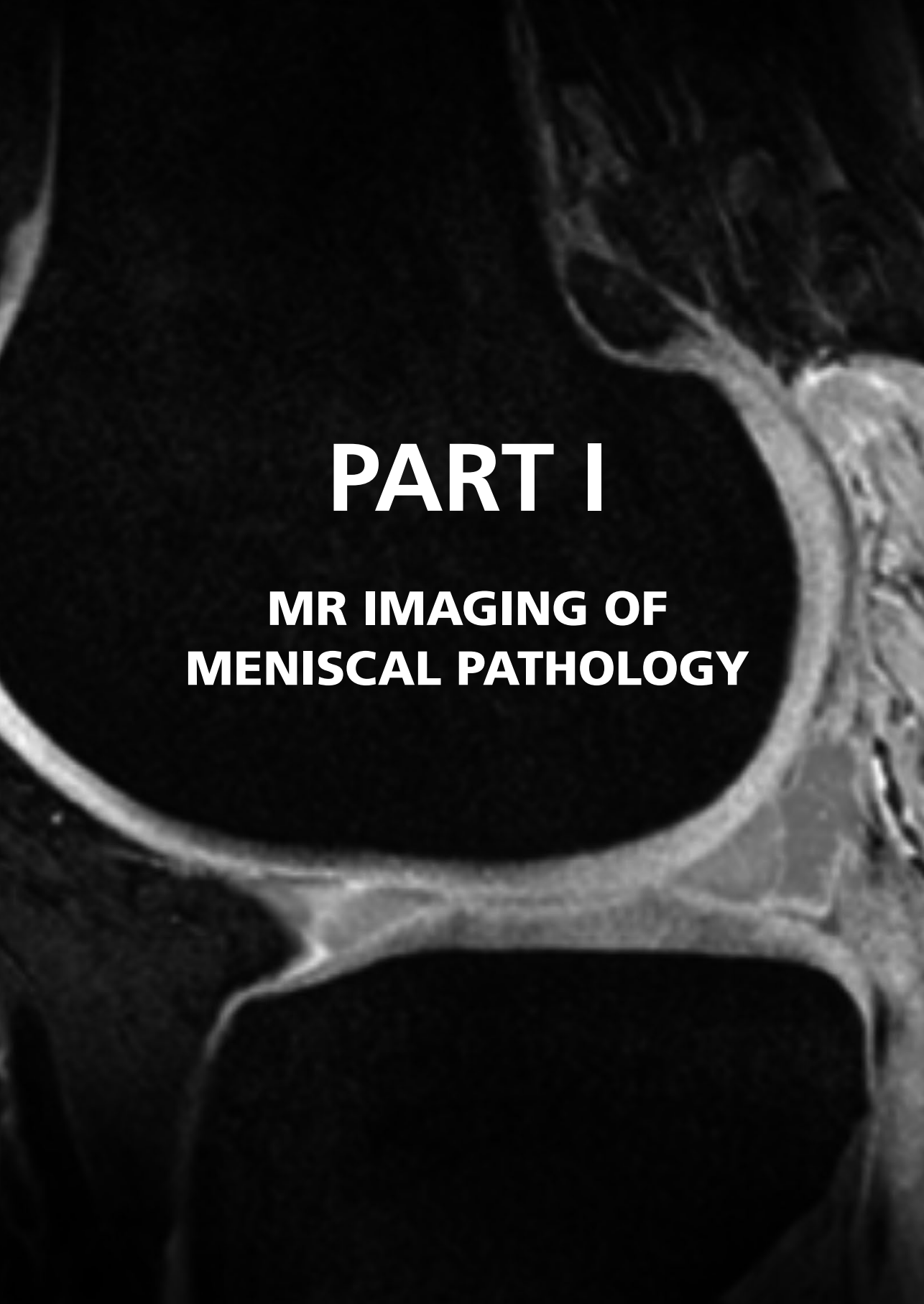
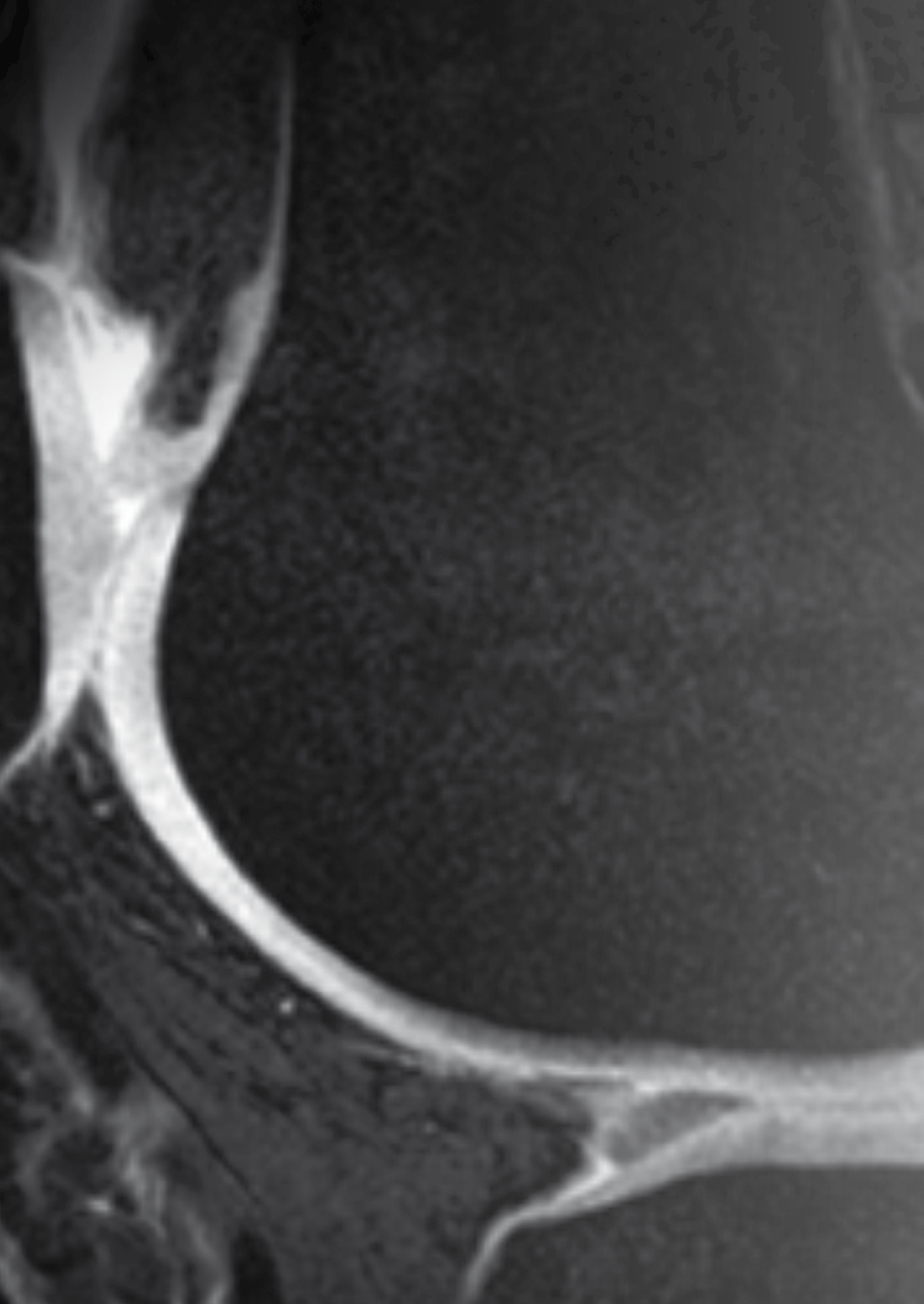


PART I

MR IMAGING OF MENISCAL PATHOLOGY



Chapter 2

T_2 mapping of the meniscus is a biomarker for early osteoarthritis

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ABSTRACT

Objective: To evaluate *in vivo* T_2 mapping as quantitative, imaging-based biomarker for meniscal degeneration in humans, by studying the correlation between T_2 relaxation time and degree of histological degeneration as reference standard.

Methods: In this prospective validation study, conducted from April 2016 to July 2017, 13 menisci from seven patients with radiographic knee osteoarthritis (median age 67 year, three males) were included. Menisci were obtained during total knee replacement surgery. All patients underwent pre-operative magnetic resonance imaging using a 3-Tesla MR scanner which included a T_2 mapping pulse sequence with multiple echoes. Histological analysis of the collected menisci was performed using the Pauli score, involving surface integrity, cellularity, matrix organization, and staining intensity. Mean T_2 relaxation times were calculated in meniscal regions of interest corresponding with the areas scored histologically, using a multi-slice multi echo postprocessing algorithm. Correlation between T_2 mapping and histology was assessed using a Generalized Least Squares model fit by maximum likelihood.

Results: The mean T_2 relaxation time was 22.4 ± 2.7 ms (range 18.5-27). The median histological score was 10, IQR 7-11 (range 4-13). A strong correlation between T_2 relaxation time and histological score was found (r_s = 0.84, 95%CI [0.64-0.93]).

Conclusion: *In vivo* T_2 mapping of the human meniscus correlates strongly with histological degeneration. T_2 mapping enables the detection and quantification of compositional changes of the meniscus, providing a non-invasive imaging biomarker for early knee OA.

INTRODUCTION

The fascinating role of the meniscus in knee osteoarthritis (OA) has attracted considerable attention among researchers for decades. Not only is meniscal damage a radiological sign of OA -up to 91% of the patients with symptomatic knee OA have coexisting meniscal tears [1]-, a torn meniscus is also one of the strongest risk factors for the development and progression of knee OA [2-5]. Although the complex role of meniscal tissue composition in the etiology of meniscal tears and the subsequent development of knee OA is not entirely clear, it has become increasingly evident that the menisci play a critical role in the long-term health of the knee joint.

Hence, the ability to objectively assess meniscal tissue quality and composition is of key importance, particularly in patients at risk for developing knee OA [2]. In order to study the etiology of meniscal tears and meniscal degeneration in knee OA development and progression, and to allow early interventions and prevention of progression, changes in meniscal tissue composition need to be detected before gross morphological changes occur.

Using conventional magnetic resonance (MR) imaging, measuring such changes in meniscal tissue composition prior to surface breakdown, is challenging. Recent developments in quantitative MR imaging techniques have made great progress in addressing this challenge [6,7]. Among quantitative MR imaging techniques, T_2 mapping is the most commonly used in knee OA research [8,9]. Based on properties of biochemical tissue components, quantitative analysis of T_2 relaxation times can reveal the composition of extracellular matrix, without the need for contrast or special MR hardware [6,10]. Increased T_2 relaxation times indicate damage to the collagen network and a decrease in water content, both signals of tissue degeneration [11].

Recent studies have shown the potential of T_2 relaxation time as biomarker to quantify meniscal degeneration in patients with knee OA [6,12-14], yet validation studies of meniscal T_2 mapping are limited. Validation of T_2 mapping, using histological analysis; the gold standard for tissue changes, was performed in one previous study [7]. In that study, T_2 mapping was performed *ex vivo*, however it is unknown how well T_2 measurements, obtained *ex vivo*, reflect the actual in vivo situation. To our knowledge, validation of *in vivo* meniscal T_2 mapping, using histological analysis as reference test, has not been performed.

We aimed to validate *in vivo* meniscal T_2 mapping in patients with knee OA by evaluating the correlation between T_2 mapping and histological reference standards for meniscal degeneration.

METHODS

Study design and participants

Our prospective observational study was conducted between April 2016 and July 2017. Meniscal specimens were obtained from patients with primary end-stage knee OA undergoing elective total knee replacement surgery at our institution. Participants were selected consecutively. Study approval was granted by the institutional Medical Ethical Committee (MEC-2012-218), and written informed consent was obtained from all participants.

Assessment of radiographic knee OA

The assessment of radiographic knee OA is described in Supplementary Material 1.

MR image acquisition

MR imaging was performed on a 3 Tesla (T) MR unit (Discovery MR750, GE Healthcare, Milwaukee, USA), 1 day prior to surgery. The MR imaging protocol included routine morphological knee sequences (Proton Density weighted sequences in sagittal, coronal and axial plane, T_2 weighted sequences with Fat Saturation (Fat-Sat) in sagittal, coronal and axial plane) and a sagittal 3D Fat-Sat fast spin echo (FSE) T_2 mapping sequence with multiple echoes. A 8-channel Send&Receive rigid dedicated knee coil (GE Healthcare, Milwaukee, WI, United States) was used. Sequence parameters are displayed in Table 1.

Table 1. MR Imaging Sequence Parameters

Scanner type	Discovery MR750, GE Healthcare, Milwaukee, WI, United States
Scanner field strength	3 T
Sequence type	3D Fast Spin Echo Fat-suppression
Matrix (RO x PE)	288 x 192
Interpolated resolution (mm^2)	0.5 x 0.8
Slice thickness / spacing	3/0
Number of slices	36
Number of echoes	5
TE (ms)	3.1; 13.4; 27.0; 40.7; 68.1
TE used for map reconstruction (ms)	3.1; 13.4; 27.0
FOV (cm)	15
Coil	8-channel S&R rigid knee coil, GE Healthcare, Milwaukee, WI, United States
Scan time (mm:ss)	09:41

Abbreviations: T = Tesla, O = readout, PE = phase encoding, TE = echo time, TR = repetition time, FOV = field of view, S&R = send and receive.

Harvesting of meniscal tissue and histological analysis

Meniscal specimens were obtained intra-operatively, during total knee replacement surgery. If present, both medial and lateral menisci were harvested, meniscal samples were stored in formaldehyde. Within three days of harvesting, menisci were cut in a standardized way according to Pauli et al. [15] (Figure 1). For each meniscus, the anterior horn and the posterior horn were processed. The menisci were cut at 45° (for the anterior horn) and 135° (for the posterior horn) angles relative to the sagittal plane (Figure 1-A). Meniscal samples were cut along two different planes: the vertical plane and the horizontal plane. The vertical section provided an overview of the longitudinally oriented collagen bundles and the tibial and femoral surfaces of the meniscus (Figure 1-C). The horizontal section, cut from the inner rim to the vascular zone at a 30° angle relative to the tibial plateau, revealed the parallel organization of the collagen bundles and matrix morphology (Figure 1-B).

The samples were fixed, dehydrated in alcohol, and infiltrated with paraffin. Next, meniscal samples were paraffin-embedded and sectioned using a microtome (MR2235, Leica-Biosystems, Wetziar, Germany) into six-micrometer sections.

To provide an overview of the overall tissue organization, and to assess border integrity, cellularity, and cell morphology, sections were stained using Hematoxylin and Eosin. Safranin O-Fast Green and Alcian Blue stain were used to evaluate proteoglycan content and mucoid degeneration, respectively. To assess collagen fiber organization, Picrosirius Red stain was used. Stained sections were visualized using (polarized-) light microscopy (Olympus-BX50, Olympus-Optical, Shinjuku, Tokyo) [16]. To assess the histological degree of degeneration, the validated, semi-quantitative Pauli score [15] was performed by two investigators with four years of experience in musculoskeletal research (Table 2). Both investigators were blinded to patient information and imaging outcomes. They examined all meniscal samples individually; in case of discrepancies, sections were assessed in consensus.

Quantitative MR image analysis

On T_2 mapping images, meniscal regions of interest (ROIs) were manually segmented by a researcher with a medical degree and four years of experience in musculoskeletal research (Figure 2), who was blinded to patient information and histology outcomes. Meniscal segmentation was performed using an image collected with the echo time (TE) showing optimal contrast between menisci and surrounding tissues (TE 7.3 ms).

Great care was taken to match MR imaging ROIs and histological ROIs. As described earlier, histological tissue processing was performed using predefined anatomical regions; the most central part of the anterior horn and the most central part of the posterior horn. As histological samples were cut in a fixed and standardized way, MR imaging ROIs were matched to histological ROIs. To do so, we identified the most central slice through the medial and lateral meniscus (defined as the sagittal slice depicting the maximum width of the anterior horn and posterior horn as individual triangles) along with the neighboring slices medially and laterally.

Table 2. Histological scoring system for meniscal degeneration by Pauli et al.	
1. Surface integrity	
Femoral surface	**Score**
• Smooth	0
• Slight fibrillation	1
• Moderate fibrillation	2
• Severe fibrillation	3
Tibial surface	
• Smooth	0
• Slight fibrillation	1
• Moderate fibrillation	2
• Severe fibrillation	3
Inner rim	
• Smooth	0
• Slight fibrillation	1
• Moderate fibrillation	2
• Severe fibrillation	3
2. Cellularity	
• Normal	0
• Hypercellularity	1
• Diffuse hypocellularity	2
• Acellular	3
3. Collagen organization/alignment and fiber organization	
• Collagen fibers organized	0
• Collagen fibers organized and foci of mucinous degeneration	1
• Collagen fibers unorganized and foci of mucinous degeneration	2
• Collagen fibers unorganized and fibrocartilaginous separation	3
4. Matrix staining (Safranin O-Fast Green)	
• None	0
• Slight	1
• Moderate	2
• Strong	3

Note: the range of possible total scores is 0 – 18. The total score can be converted to a grade as follows: grade 1 = 0-4 (normal), grade 2 = 5-9 (mild degeneration), grade 3 = 10-14 (moderate degeneration), grade 4 = 15-18 (severe degeneration). In the present study, the Pauli score was used as continuous measure; no conversion to grades was performed.

Four ROIs were defined per patient: the anterior and posterior horn of the medial and lateral meniscus. All ROIs consisted of three consecutive slices: the most central slice along with the adjacent slice medially and laterally. MR imaging scout views, using T_2 weighted images in the coronal and axial plane, were used to verify that the ROIs were correctly defined (i.e. that they matched histological ROIs).

For MR image post-processing, in-house developed registration and fitting algorithms in Matlab (R2011a; The MathWorks, Natick, Mass) were used [17]. Automated rigid registration in 3D was used for motion compensation [17]. Similar to previous studies [18,19], we excluded all images with TE above 30 ms because of the very low signal-to-noise-ratio in meniscal tissue (Table 1). To reduce effects of possible outliers within ROIs, T_2 relaxation times were weighted by the reciprocal of the uncertainty of the estimated T_2 relaxation time in each voxel. This

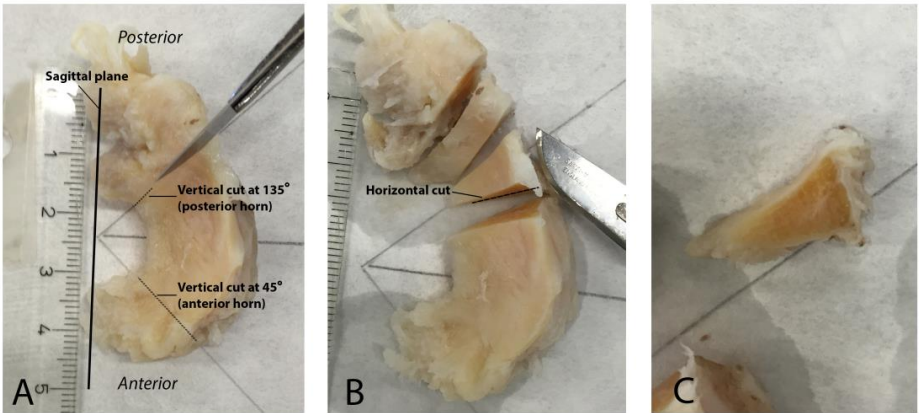

Figure 1. Preparation of meniscal samples. Example of a grossly intact lateral meniscus harvested during total knee arthroplasty in a left knee of a 59-year-old female with medial compartment knee OA (Kellgren and Lawrence grade 4). A) Cutting the meniscus according to the method of Pauli et al; vertical cut. B) Horizontal cut, from the inner rim to the vascular zone at a 30° angle relative to the tibial plateau. C) Detail view of vertical cut of the posterior horn.

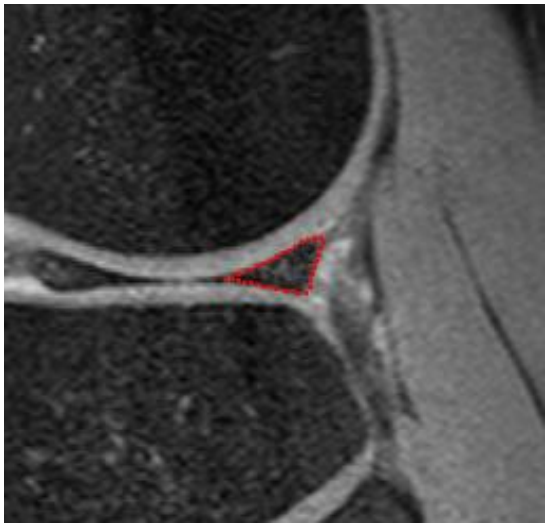

Figure 2. Segmentation of the meniscus. Representative example of sagittal T_2 mapping image with manually drawn region of interest (ROI) of the posterior horn of the lateral meniscus in a 67-year-old female with knee osteoarthritis.

uncertainty was measured with the square root of the Cramer-Rao lower bound, which gives a lower bound for the standard deviation of the estimated T_2 relaxation time [17]. The weighted T_2 mapping relaxation times for each ROI were averaged over the three consecutive MR imaging slices, further referred to as mean T_2 relaxation time [17].

Statistical analysis

Descriptive statistics for all available variables, including demographics, T_2 relaxation times per meniscal ROI, and histological scores, are reported. Normality was tested using Shapiro-Wilk tests. Normally distributed data were presented as mean with standard deviation; non-normally distributed data were presented as median with inter quartile range (IQR).

Inter-observer reliability of histological scoring was tested using two-way intraclass correlation coefficients (ICCs) of absolute agreement, taking single measurements.

We performed a linear mixed-effects model to assess the correlation between T_2 relaxation times and histological scores, where T_2 relaxation times were considered as dependent variable and histological score as independent variable. We employed Generalized Least Squares function in the "nlme"-library in the statistical software "R" [20] allowing to calculate the correlation in repeated measures data (i.e. in datasets that include multiple measures per patient). Age, BMI, and sex were tested as potential covariates since they might impact T_2 values. A backward variable selection and the likelihood ratio test were used for this purpose. Subgroup analyses were performed using a linear mixed-effects model, regarding regional differences.

Statistical analyses were performed using R version 3.4.2 (2017) [20].

RESULTS

Patient characteristics

In total, 13 menisci were collected from 7 patients with knee OA; six medial and seven lateral menisci. There was a slight overall female predominance of 57%, the median age of patients was 67 years (range 59-74). None of the menisci showed a macroscopic tear. Patient characteristics are shown in Table 3.

Radiographic knee OA

Patients had either moderate radiographic knee OA (KLG 3, n = 3) or severe radiographic knee OA (KLG 4, n = 4).

T_2 relaxation time in meniscal tissue

The mean meniscal T_2 relaxation time was 22.4 ± 2.7 ms (range 18.5-27). In addition to overall mean T_2 relaxation times (i.e. the mean of measurements from all ROIs), mean T_2 relaxation times were calculated for the four meniscal ROIs (medial anterior and posterior, lateral anterior and posterior) separately, reported in Table 4. Highest T_2 relaxation times were found in the medial anterior horn of the meniscus. Statistical significantly higher T_2 relaxation times were found in the medial menisci than in the lateral menisci ($P = 0.005$). No statistically significant differences between the anterior and posterior meniscal horns in T_2 relaxation time were found ($P = 0.14$). Representative T_2 mapping findings are displayed in Figure 3-I – 3-J.

Table 3. Characteristics of the Study Population		
No. of patients		7
No. of menisci		13
Age (y)*		67 (59-74)
Female patients		
	No. of patients	4
	Median age (y)	66
	Age range (y)	59-67
Male patients		
	No. of patients	3
	Median age (y)	73
	Age range (y)	66-74
Body Mass Index† (kg/m^2)		28 ± 4
Time interval between MR imaging and harvesting† (days)		1 ± 0
Radiographic OA grade		KL grade 3: n = 3 KL grade 4: n = 4
Most affected side of radiographic knee OA		Medial compartment: n = 6 Lateral compartment: n = 1
Patients with meniscal tear		0

* Data are median values (range)
† Data are mean values ± standard deviation
Abbreviations: OA = osteoarthritis, KL = Kellgren and Lawrence

Table 4. Meniscal T_2 Measurements and Histological Scores per ROI		
	T_2 (ms)*	Histological Score†
Medial meniscus, anterior	25.4 ± 1.5	12, 11-12
Medial meniscus, posterior	23.2 ± 2.6	10, 8.5-11.5
Lateral meniscus, anterior	20.8 ± 1.4	7, 6-8
Lateral meniscus, posterior	19.9 ± 1.2	8, 5-8

* Data are mean values ± standard deviations
† Data are median values, inter quartile range
Abbreviations: ROI = region of interest, ms = milliseconds

Histological findings in meniscal tissue

In two patients, all four meniscal regions (medial anterior, medial posterior, lateral anterior and lateral posterior) could be harvested. In the remaining five patients, as a result of partial maceration of the menisci due to end-stage knee osteoarthritis, not all four regions could be harvested (only three regions possible in four patients and a single region in one patient). In total, 21 meniscal regions were used for histological analysis.

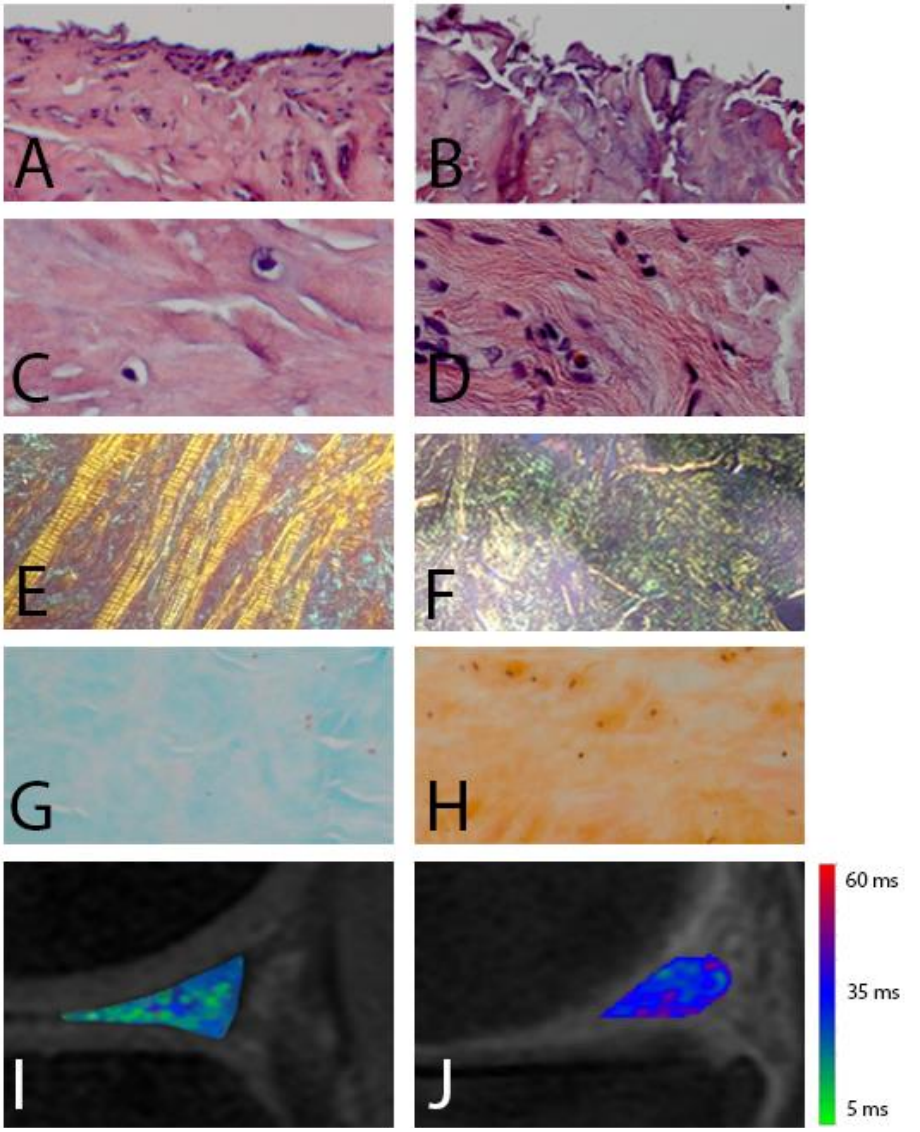

Figure 3. Representative images of histological findings and corresponding T_2 mapping images. A, C, E, G) Posterior horn of lateral meniscus of a 67-year-old female with knee OA (Kellgren and Lawrence grade 3), with a mean T_2 relaxation time of 18.6 ms and a histological score of 5. B, D, F, H) Posterior horn of medial meniscus of a 66-year-old female with knee OA (Kellgren and Lawrence grade 4) with a mean T_2 relaxation time of 26.9 ms and a histological score of 13. A, B) Surface integrity (HE staining, 10 x zoom). C, D) Cellularity (HE staining, 40 x zoom). E, F) Collagen organization (Picrosirius-Red staining, 5 x zoom). G, H) Collagen matrix staining intensity, a decreased intensity of green staining indicates disruption in collagen matrix (Saf-O-Green staining, 10 x zoom). I, J) Corresponding non-contrast sagittal T_2 mapping images with color map of the meniscus. The color bar on the right shows the range of T_2 values.

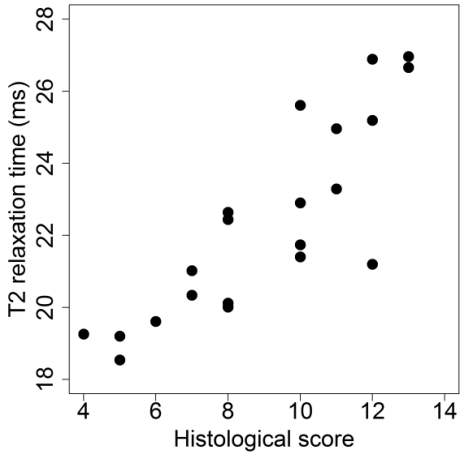

Figure 4. Scatterplot of histological scores versus T_2 relaxation times, in all patients and all measurements.

The inter-observer reliability of histological scoring between the two observers was excellent (ICC: 0.95, 95%CI [0.79-0.99]). We found an overall median histological score of 10, IQR 7-11 (range 4-13). Mean histological scores per meniscal ROI are shown in Table 4. As for T_2 relaxation times, the highest histological scores were found in the medial anterior horn of the meniscus and histological scores were found to be higher in the medial menisci than in the lateral menisci (P = 0.007). Also, no statistically significant differences between the anterior and posterior meniscal horns in histological score were found (P = 0.20). Representative histological findings are displayed in Figure 3-A - 3-H.

Correlation between T_2 mapping and histological scores

In the linear mixed-effects model, the variables age, sex and BMI were not statistically significant and were excluded from the model. To incorporate the potential effect of repeated measures (i.e. multiple measures per patient), the model has been statistically adjusted. A strong correlation between T_2 mapping and histology (correlation coefficient 0.85, 95%CI [0.68-0.93]) was found.

DISCUSSION

In this study, we assessed the correlation between *in vivo* meniscal T_2 mapping and histology in patients with radiographic knee OA. We demonstrated that meniscal T_2 relaxation times in patients with knee OA show a strong correlation with the degree of histological degeneration. These findings indicate the potential of T_2 relaxation times, obtained with *in vivo* T_2 mapping, as non-invasive imaging biomarker for meniscal degeneration.

The results of our study are in line with those of previous research on meniscal T_2 mapping where no histological analysis was performed. These studies showed that T_2 mapping can differentiate between healthy patients and those with knee OA. Zarins et al. found that meniscal T_2 mapping discriminated between healthy and severe OA, but not between healthy and mild OA, and only in the posterior meniscal horns [19]. Rauscher and colleagues reported that T_2 mapping discriminated between healthy, mild and severe OA in all meniscal regions [13]. In addition to OA patients, T_2 mapping has been investigated in patients with acute knee injury. Significantly higher T_2 relaxation times were reported in patients with an anterior cruciate ligament rupture, compared to healthy controls [12].

To our knowledge, this is the first study to investigate the validity of in vivo meniscal T_2 mapping in osteoarthritic patients, using histology as the reference test. Recently, Nebelung et al. performed a validation study of multiple quantitative MR imaging techniques, including T_2 mapping [7]. Histological analysis of meniscal samples from total knee replacement surgeries was used as the reference standard. In contrast to the present study, their T_2 mapping measurements were performed *ex vivo*. Whether T_2 measurements, obtained *ex vivo*, reflect the actual *in vivo* situation, could be questioned. Several factors in *ex vivo* experiments may affect T_2 relaxation times. First, storage of meniscal samples in medium and changes in tissue hydration may have potentially affected T_2 measurements [7,14]. Second, in *ex vivo* experiments, samples are typically scanned at room temperature and not at body temperature, potentially influencing T_2 relaxation times. Last, *ex vivo* quantitative MR imaging experiments usually have different acquisition parameters, such as the number and duration of echo times, field of view, and acquisition matrix, compared with *in vivo* [7,21]. These factors may have caused the lower correlation coefficient (*r*: 0.65) between T_2 mapping and histology in their study compared to ours.

In musculoskeletal imaging research, T_2 mapping was originally developed for the quantification of articular cartilage, yet T_2 relaxation times have been increasingly used to assess meniscal tissue composition [7,13,14,19]. It is suggested that meniscal T_2 mapping can be challenging due to the short T_2 components and the heterogeneity of meniscal tissue [22,23]. In previous studies, concerns have therefore been raised that standard spin echo based T_2 mapping is not suitable to quantitatively measure the menisci [24]. The results of the present study, however, suggest that in vivo spin echo based T_2 mapping can provide accurate T_2 measurements in menisci. An important advantage of T_2 mapping is that it has the potential to quantitatively assess a variety of knee tissues; as the range of echo times in T_2 mapping is usually wide [25,26]. Quantitative MR imaging techniques that obtain extremely short echo times, such as Ultrashort echo time-enhanced T_2* (UTE-T_2*) are less suitable for the assessment of, for example, superficial layers of articular cartilage, due to their higher T_2 signal [6,27]. Taking into account that knee OA is a complex multi-tissue disease, involving the whole joint, T_2 mapping has the best potential for quantifying knee OA [6,25].

The results of the present study suggest that T_2 relaxation times, obtained with *in vivo* T_2 mapping, can potentially be used as non-invasive biomarker to detect early changes in meniscal tissue that indicate degeneration. Given the important role of the menisci in the long-term health of the knee joint, such biomarkers for meniscal tissue quality and degeneration are of great value. The detection of early meniscal tissue changes, indicating degeneration, would allow a better understanding of the etiology and development of knee OA. Furthermore, it would allow the identification of patients at early OA stages, before irreversible damage occurs. Also, it would improve the monitoring of disease progression and treatment response. The long-term goal would be to allow the detection and monitoring of early meniscal tissue changes that indicate an increased risk for knee OA, potentially enabling early treatment strategies for knee OA.

In conclusion, *in vivo* T_2 mapping of the human meniscus provides accurate measurements of meniscal degeneration in patients with knee osteoarthritis. By quantifying subsurface meniscal changes, T_2 mapping potentially provides a non-invasive imaging biomarker for meniscal degeneration.

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Disclosures of conflicts of interest:

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SUPPLEMENTARY MATERIAL 1: ASSESSMENT OF RADIOGRAPHIC KNEE OA

The degree of radiographic knee osteoarthritis was graded according to the Kellgren and Lawrence (KL) classification system ranging from 0 (no OA) to 4 (end stage OA). The KL classification includes the assessment of joint space narrowing, osteophytes, subchondral sclerosis, and deformity of bone contour. Grading was performed by a musculoskeletal radiologist with 12 years of experience, using weight bearing anteroposterior radiographs. Radiographs and MR imaging scans were acquired on the same day.

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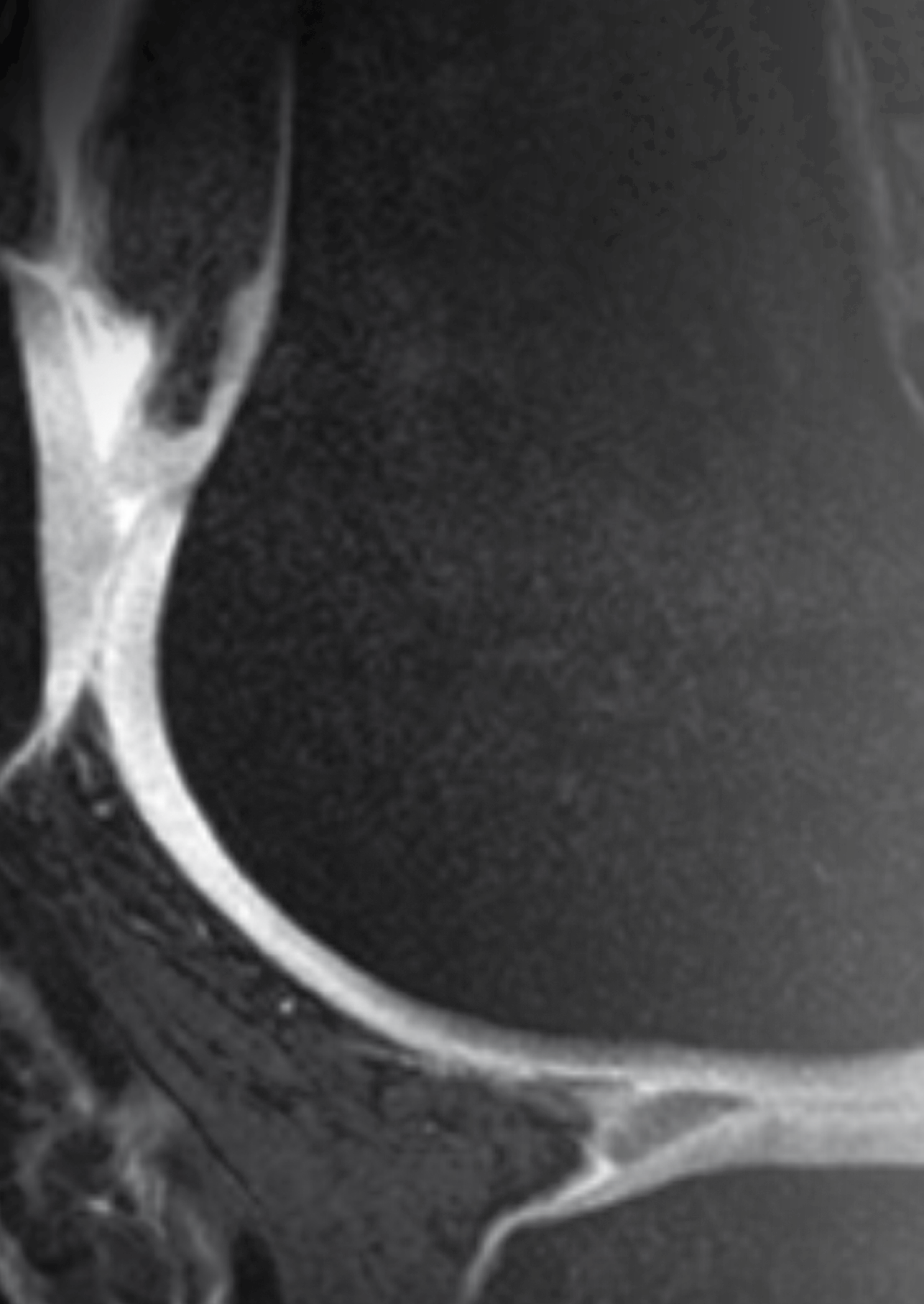

Chapter 3

T_2 mapping of knee cartilage: multicenter multivendor reproducibility

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ABSTRACT

Objective: T_2 mapping is increasingly used to quantify cartilage degeneration in knee osteoarthritis, yet multicenter reproducibility studies of cartilage T_2 mapping are limited. The purpose of this study was to determine the longitudinal reproducibility and multicenter comparability 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, over 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). A T_2 phantom was scanned once at each center. To evaluate longitudinal reproducibility, ICC, RMS-CV, and Bland-Altman plots were used. To assess comparability of in vivo and phantom T_2 values across centers, ANOVA was performed.

Results: ICCs of overall T_2 measurements (all centers pooled), in each ROI ranged from 0.73 to 0.91, indicating a good to excellent longitudinal reproducibility. RMS-CVs in each ROI ranged from 1.1% to 1.5%. The overall RMS-CV (all ROIs pooled) in each center ranged from 0.6% to 1.6%. Bland-Altman plots revealed that none of the centers showed a systematic error. Significant differences in absolute T_2 values were observed across centers, both in vivo and in the phantom.

Conclusion: The results of this study indicate 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 [1]. 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 [2]. T_2 mapping, which provides a marker for collagen integrity without the need for intravenous contrast or specific MRI hardware [2-5], is the most widely used qMRI technique in knee OA research [5,6].

Although cartilage T_2 mapping has found wide-spread use in OA research [7], reproducibility studies on T_2 mapping in a multicenter setting are scarce. Longitudinal reproducibility analyses of multicenter cartilage T_2 mapping have been limited to studies using similar scanners and harmonized MRI acquisition protocols [5,8,9]. 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 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 reproducibility and multicenter comparability of T_2 mapping of different cartilage regions, using various MRI systems, field strengths and acquisition protocols.

METHODS

Study design

In this prospective observational study, five medical centers located in different geographical parts of The Netherlands participated. In these centers, a multicenter randomized controlled trial is currently conducted, in which T_2 mapping is used as an outcome measure for deterioration of knee cartilage two years after a meniscal tear. 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 comparability of T_2 values across centers, cross-validation was performed at baseline in human subjects as well as a phantom. Approval from the Institutional Review

Board of our institution [number deleted to maintain the integrity of the review process]. 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 for cross-validation of 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 [1]. Phantom stability was verified (ICC 0.90, 95%-CI [0.856–0.928] over a 5-month-interval).

Data acquisition

MRI acquisition parameters, stratified per center, are summarized 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 [10]. 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 [initials deleted to maintain the integrity of the review process]. 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). 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 [10]. The automated registration of the T_2 mapping scan to the high-resolution scan at follow-up 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.

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

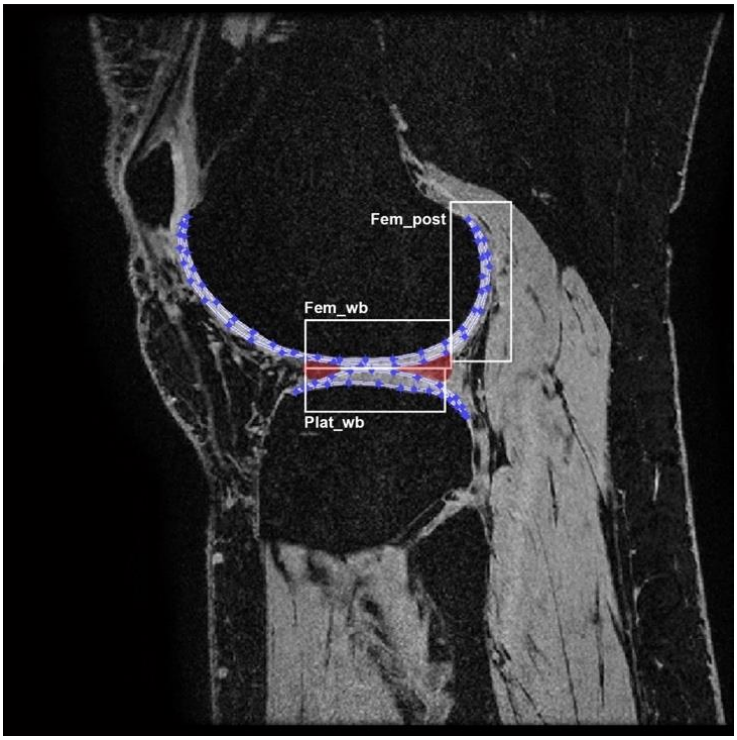

Figure 1. Cartilage segmentation on sagittal high-resolution FSPGR image, lateral compartment. Blue dotted lines surround the segmented mask; white boxes represent the ROIs. Abbreviations: Fem_post = posterior femoral condyle; Fem_wb = weight-bearing femoral condyle; Plat_wb = weight-bearing tibial plateau; FSPGR = fast spin gradient echo; ROI = region of interest.

Statistical analysis

The longitudinal reproducibility of T_2 measurements in each cartilage ROI was evaluated with intraclass correlation coefficients (ICCs) for absolute agreement of single measures, using a two-way random model, by pooling 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 [11].

In addition, we calculated coefficients of variation (CVs, defined as the standard deviation (SD) normalized by the mean value of the measurements) of differences in T_2 measurements between baseline and follow-up for each subject. Since averaging the subject's CVs to obtain pooled CVs for each center and for each cartilage ROI is inadequate [12,13], we calculated the root-mean-square coefficient of variation (RMS-CV, expressed as a percentage) according to the method of Gluer et al. [12]. 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. Bland-Altman plots were obtained for each center 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. The smaller the range between these two limits, the higher the reproducibility.

For cross-validation of T_2 mapping across centers, we calculated pooled T_2 values from all subjects, as well as phantom T_2 values, for each center. Data was tested for normality using Shapiro-Wilk tests. Between-center differences in T_2 values were analyzed using one-way ANOVA with Dunn's Multiple Comparison Test. 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

Mean T_2 values and longitudinal reproducibility outcomes of human subjects for each cartilage ROI are presented in Table 2. ICCs of T_2 measurements pooled across all centers ranged from 0.73 to 0.91 for the different ROIs, indicating a good to excellent reproducibility. When pooling the longitudinal T_2 values of all ROIs across all centers, we found an excellent reproducibility (ICC 0.90, 95% confidence interval [0.856–0.928]). The RMS-CVs in each ROI ranged from 1.1% to 1.5%, Bland-Altman plots of these measurements showed

Table 2. In vivo T2 values and longitudinal reproducibility per cartilage ROI

	Baseline		6-months FU		Agreement		
	T2† (ms)	CI-95	T2† (ms)	CI-95	ICC‡	CI-95	RMS-CV (%)
Femoral cartilage							
Weight-bearing							
Medial	46.3	42.6 - 50.0	47.2	43.1 - 51.3	0.91	0.78 - 0.96	1.3
Lateral	47.9	44.4 - 51.4	48	44.6 - 51.3	0.82	0.59 - 0.92	1.3
Posterior							
Medial	47	43.5 - 50.4	46	42.5 - 49.6	0.91	0.80 - 0.97	1.1
Lateral	43.9	40.1 - 47.7	42.8	39.7 - 45.8	0.85	0.66 - 0.94	1.2
Tibial cartilage							
Medial	40.8	38.0 - 43.6	41.9	37.9 - 45.8	0.86	0.69 - 0.94	1.4
Lateral	34.5	32.3 - 36.7	35.2	32.8 - 37.5	0.73	0.44 - 0.89	1.5

† Mean T2 relaxation times of human volunteers, pooled across all centers

‡ intraclass correlation coefficient of absolute agreement, single measurements

Abbreviations: ROI = region of interest, FU = follow-up, ICC = Intraclass Correlation Coefficient, CI-95 = 95% confidence interval, RMS-CV = root mean square coefficient of variation

Table 3. RMS-CV of longitudinal in vivo T2 measurements per cartilage ROI

	Center 1	Center 2	Center 3	Center 4	Center 5
Femoral cartilage					
Weight-bearing					
Medial	1.6	3.4	5.2	1.2	0.9
Lateral	3.3	2.2	3.3	4.2	1.3
Posterior					
Medial	1.5	4.0	2.3	1.2	2.0
Lateral	1.1	6.2	2.4	2.9	1.1
Tibial cartilage					
Medial	2.7	1.8	4.0	4.5	1.4
Lateral	2.8	1.2	2.7	6.2	1.1
Overall (all ROIs pooled)	1.1	1.3	1.4	1.6	0.6

Note: 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. Abbreviations: RMS-CV = root mean square coefficient of variation, ROI = region of interest

no systematic error (data not shown). Table 3 summarizes the RMS-CVs of longitudinal T_2 measurements per center. The overall (all ROIs pooled) RMS-CV in each center ranged from 0.6% to 1.6%. Bland-Altman plots for each center revealed mean differences between overall (all ROIs pooled) baseline and follow-up T_2 measurements ranging from 0.03 to 2.70 ms (Figure 2). Lowest mean differences and narrowest confidence intervals were observed in center 1 and center 5, indicating highest reproducibility. None of the centers showed a systematic error.

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 ms). 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 comparability of *in vivo* and phantom T_2 measurements

In Figure 3-A, T_2 values of all cartilage ROIs pooled are plotted per center, showing discrepancies in pooled T_2 values across centers. A statistically significant difference in pooled 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 (Figure 3-A). An identical pattern of mutual differences in T_2 values among subjects was observed at follow-up (data not shown). 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 3-B).

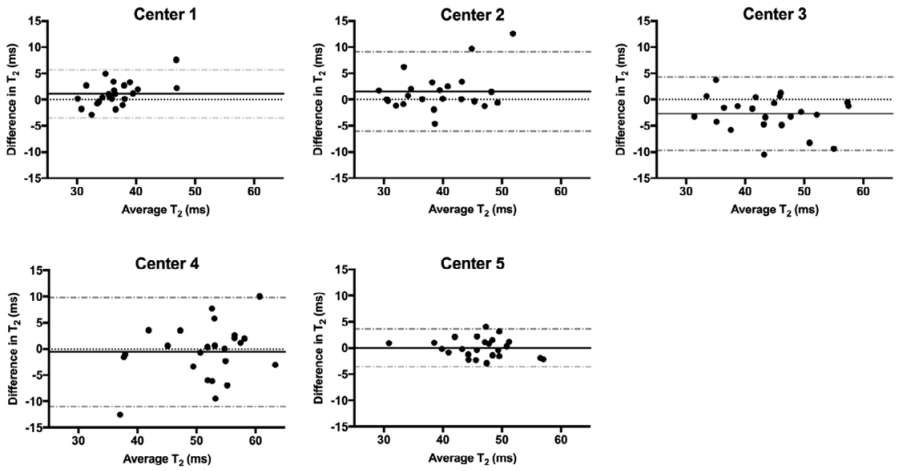

Figure 2. Bland-Altman plots showing the differences in *in vivo* T_2 values between baseline and follow-up against the mean T_2 values in each center. The bold line represents the mean difference, dotted lines represent limits of agreement. Note the pattern and dispersion of the black dots in relation to the mean difference in each center, indicating a random error rather than than a systematic error, and the differences in limits of agreement across centers. The narrower the limits, the higher the reproducibility of measurements.

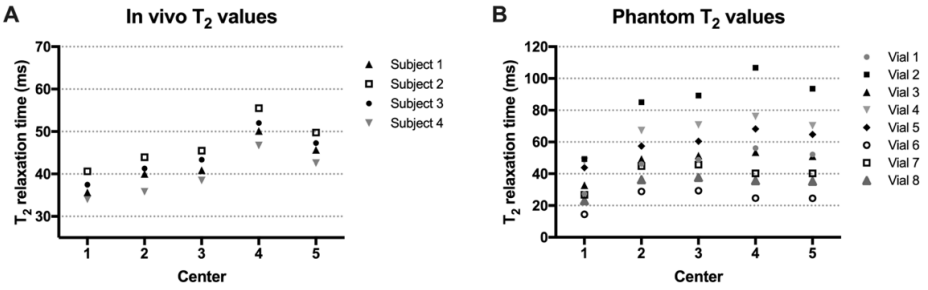

Figure 3. Mean T_2 values pooled across all cartilage regions of interest (ROIs), acquired at baseline. A) *In vivo* T_2 values plotted per subject for each center. B) Phantom T_2 values plotted per vial for each center. The concentration of manganese chloride for each vial was: vial 1 = 0%; vial 2 = 5%; vial 3 = 10%; vial 4 = 15%; vial 5 = 20%; vial 6 = 30%; vial 7 = 50%; and vial 8 = 80%.

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 comparability of T_2 measurements in different cartilage ROIs in a multicenter setting, using various MRI systems and acquisition protocols.

In our multicenter study, ICCs for longitudinal T_2 measurements ranged from 0.73 to 0.91 with RMS-CVs (of pooled ROIs) 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 compare favorably with a previous single center reproducibility study [9], using a Philips 3-Tesla scanner, reported RMS-CVs (from pooled ROIS) of 3.2% - 6.3% over a 2-month-interval. A multicenter, single vendor study by Li et al. [8], evaluated longitudinal reproducibility of cartilage T_2 values of two traveling subjects acquired at two locations with similar types of MRI scanner (GE 3T) and sequence parameters over a 10-month-interval. In the latter study, a pooled 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 [5]. Longitudinal cartilage T_2 measurements were evaluated by pooling 50 subjects, involving patients with OA and asymptomatic control subjects, from five centers using different MRI vendors (Philips and Siemens). 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 narrowest confidence intervals. 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 [14].

Many factors can potentially cause longitudinal variation in T_2 measurements, apart from biological changes. These include environmental factors (e.g. MRI room temperature), up-

grades in MRI hardware or software, changes in phantom composition, subject features (exercise, knee flexion), and diurnal variation in T_2 measurements [8,9]. 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 comparability of cartilage T_2 measurements [9]. 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 [15,16], in particular the use of receive only versus transmit and receive coils. 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 [15], similar to our findings. Second, magnetic field strength among centers varied in our study, potentially influencing T_2 values [17,18]. 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. [14], the influence of different T_2 mapping sequence protocols in a single scanner was assessed. 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. [19], 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. 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 there-

fore 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 some 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 limited sample size was feasible. Consequently, this study was statistically underpowered to report ICCs for longitudinal reproducibility of each center individually. Second, as our study was limited to healthy subjects, it is not sure whether these findings are generalizable to OA subjects.

Conclusion

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 interpret cautiously considering the size and nature (i.e. healthy subjects) of the sample. Given the differences in T_2 values across centers, absolute T_2 values obtained in various centers in multicenter multivendor clinical trials should not be pooled.

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Competing interest statements

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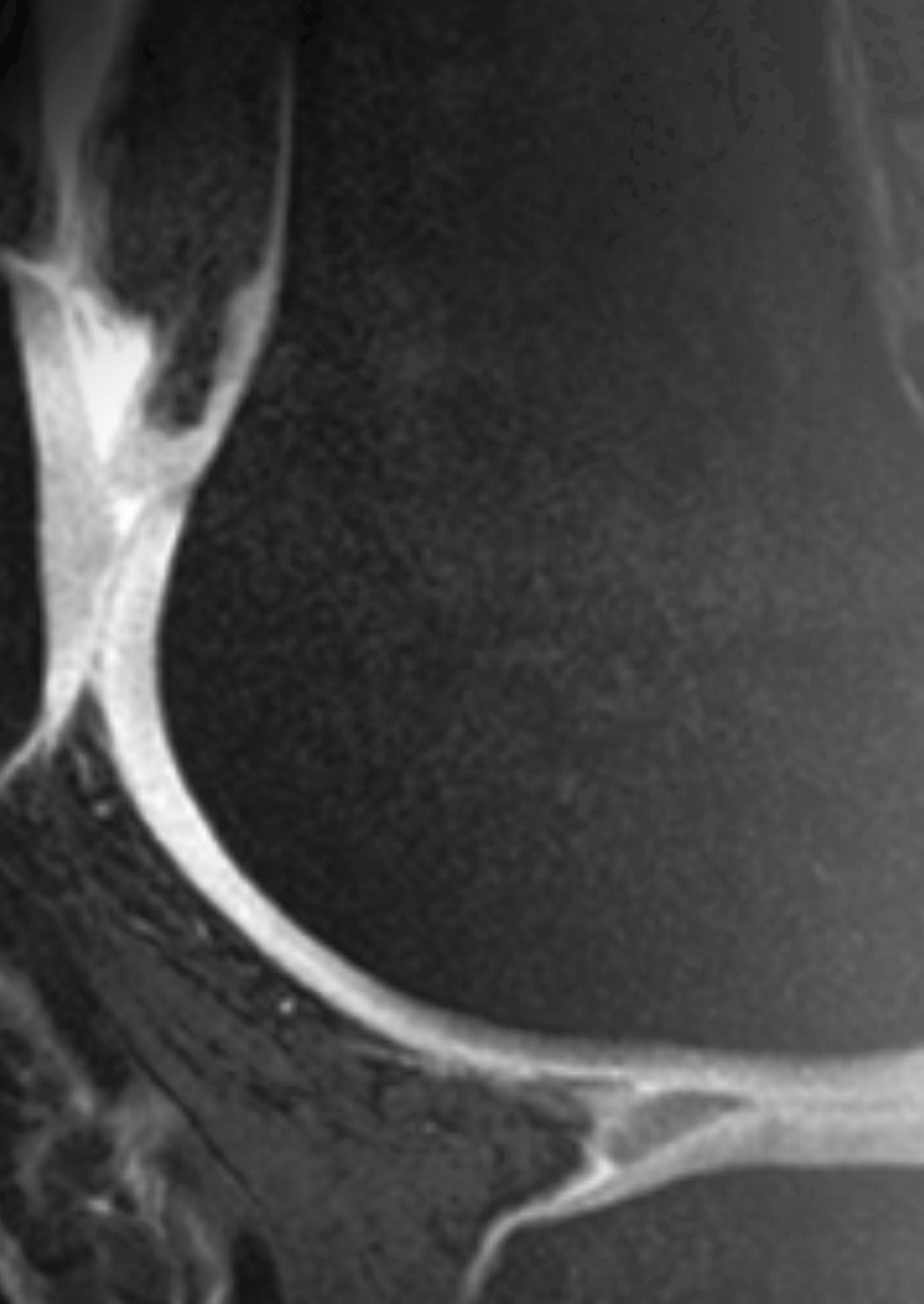

Chapter 4

Time-saving opportunities in knee osteoarthritis: structural imaging and T_2 mapping in the knee using a single 5-minute MRI scan

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ABSTRACT

Objective: To assess the discriminative power of a 5-minute quantitative double-echo steady-state (qDESS) sequence for simultaneous T_2 measurements of cartilage and meniscus, and structural knee osteoarthritis (OA) assessment, in a clinical OA population, using radiographic knee OA as reference standard.

Methods: 53 subjects were included, divided over three groups based on radiographic and clinical knee OA: 20 subjects with no OA (Kellgren-Lawrence Grade (KLG) 0), 18 with mild OA (KLG2) and 15 with moderate OA (KLG3). All patients underwent a 5-minute qDESS scan. We measured T_2 relaxation times in four cartilage and four meniscus regions-of-interest (ROIs) and performed structural OA evaluation with the MRI Osteoarthritis Knee Score (MOAKS) using qDESS with multiplanar reformatting. Between-group differences in T_2 values and MOAKS were calculated using ANOVA. Correlations of the reference standard (i.e., radiographic knee OA) with T_2 and MOAKS were assessed with correlation analyses for ordinal variables.

Results: In cartilage, mean T_2 values were 36.1 ± SD 4.3, 40.6 ± 5.9 and 47.1 ± 4.3 ms for no, mild, and moderate OA, respectively ($P<0.001$). In menisci, mean T_2 values were 15 ± 3.6, 17.5 ± 3.8 and 20.6 ± 4.7 ms for no, mild, and moderate OA, respectively ($P<0.001$). Statistically significant correlations were found between radiographic OA and T_2 and between radiographic OA and MOAKS in all ROIs ($P<0.05$).

Conclusion: Quantitative T_2 and structural assessment of cartilage and meniscus, using a single 5-minute qDESS scan, can distinguish between different grades of radiographic OA, demonstrating the potential of qDESS as an efficient tool for OA imaging.

INTRODUCTION

The growing population suffering from knee osteoarthritis (OA) and the lack of early biomarkers and therapeutics prompt the need for efficient imaging methods [1]. Magnetic resonance imaging (MRI) allows assessment of the whole knee joint, making it ideally suited for imaging in knee OA, which is a multi-tissue disease [2,3]. Several potential MRI-based biomarkers have been proposed in this context [4]. In particular, the role of quantitative MRI (qMRI) techniques is emerging. qMRI techniques, such as T_2 mapping, have the ability to non-invasively detect subtle changes in biochemical composition of tissues such as cartilage and menisci. Increased T_2 relaxation times have been shown to be associated with cartilage and meniscus degeneration, potentially enabling early stage detection of knee OA and similar conditions [5-8]. T_2 mapping does not require a contrast injection or special MRI imaging hardware and numerous techniques for post-processing of T_2 images are available [5,7,9,10].

Besides quantitative MR imaging, structural evaluation of the knee is fundamental in the assessment of knee OA, given its multi-tissue nature [2,3]. The semi-quantitative MRI Osteoarthritis Knee Score (MOAKS) [11] is a widely used and well-validated instrument for evaluating knee OA, and has been applied in large scale epidemiological OA studies such as the Osteoarthritis Initiative (OAI) [11-14].

T_2 mapping and MOAKS are potential biomarkers to non-invasively assess joint health; however, acquiring them efficiently is a challenge. In general, multiple sequences are used in knee OA imaging, often resulting in time consuming MRI protocols that take 30-45 minutes or longer [6,15]. In particular, in the context of large-scale clinical trials and repeated measurements, MRI acquisition can create a significant burden for patients, hospitals, and research budgets. In the context of quantitative MRI, multiple sequences also bring up the need for registration between sequences. Hence, creating more streamlined MRI protocols and reducing acquisition time is of great interest.

In the present study, we evaluated a novel MRI technique to reduce scan time in the context of knee OA: the quantitative double-echo steady-state (qDESS) sequence. qDESS generates two echoes: one echo with T_1/T_2 weighting (resembling proton-density contrast), and one echo with T_2 weighting. It has the potential to provide diagnostic images as well as quantitative measurements (i.e., T_2 maps) of the knee in a single sequence with an acquisition time less than five minutes [16,17].

Proof-of-concept of qDESS for T_2 mapping of cartilage and meniscus and structural knee assessment (using MOAKS) has been provided by Chaudhari et al. [16]. Focusing on healthy subjects, they validated qDESS against routine methods for T_2 measurements and MOAKS and reported high accuracy in most tissues. Also, a pilot study in 10 patients with knee OA, performed in the same work, provided promising qDESS-based T_2 mapping and MOAKS outcomes, suggesting that accurate knee OA measurements are possible with qDESS [16]. Building upon this work, we further assessed the discriminative power of quantitative and

structural qDESS-based biomarkers, in a larger OA cohort against radiography, widely accepted as the gold standard for knee OA imaging [18,19]. We evaluated structural MOAKS scores and T_2 measurements of the knee cartilage and meniscus in a clinical OA population. In contrast to the approach of Chaudhari and colleagues, which comprised a global assessment of cartilage and menisci, in the present study we evaluated predefined subregions of cartilage and menisci. Regional assessment is relevant as knee OA is a focal disease with an heterogenous disease pattern [6,20,21].

The aim of the present study was to assess the discriminative power of a single 5-minute qDESS MRI sequence for simultaneous T_2 measurements of cartilage and meniscus, and structural knee OA assessment, in a clinical osteoarthritis population, using radiographic knee OA as a reference standard.

METHODS

Study population

This study was performed with approval from our Institutional Review Board and in compliance with Health Insurance Portability and Accountability Act (HIPAA) regulations. Written informed consent was obtained from all participants after receiving full explanation about the study. Consecutive patients who were referred by the Department of Orthopedic Surgery for knee MRI at Stanford Medical Center between December 2016 and July 2017 were screened for eligibility. The eligibility criteria for this study are shown in Table 1. Based on radiographic (Kellgren and Lawrence grade (KLG) [22]) and clinical (American College of Rheumatology (ACR) criteria [23]) degree of knee OA, three subject groups were selected: subjects with no

Table 1. Eligibility criteria

Non-OA subjects	OA-subjects
Referred for knee MRI	Referred for knee MRI
No contra-indication for MRI	No contra-indication for MRI
AP weightbearing radiograph of index knee[a] available	AP weightbearing radiograph of index knee[a] available
No ACL reconstruction in index knee in medical history	No ACL reconstruction in index knee in medical history
KLG0	KLG2 or KLG3
	Knee pain + at least 1 of 3: 1, Age > 50 years 2. Stiffness < 30 minutes 3. Crepitus

a Acquired within 2 weeks before or after MRI acquisition
Abbreviations: OA = osteoarthritis, MRI = magnetic resonance imaging, AP = anteroposterior, ACL = anterior cruciate ligament, KLG = Kellgren Lawrence grade

OA (KLG0 and ACR negative), subjects with mild OA (KLG2 and ACR positive), and subjects with moderate OA (KLG3 and ACR positive).

Scoring of radiographic knee OA

The assessment of radiographic knee OA was performed according to the KLG criteria [22], by a researcher with a medical degree and four years of experience in musculoskeletal imaging research (SE) who was blinded to any patient data. Standardized, weight-bearing AP radiographs were used. A second reader, a musculoskeletal radiologist with 15 years of experience (EO) also performed the KL grading in a random selection of 20 subjects from the study population to assess interobserver reliability. To assess intra-observer reliability of the primary observer (SE) 20 randomly selected subjects from the study population were re-evaluated 14 days after initial grading.

MR imaging data acquisition

MR imaging was performed on one of two identical 3-Tesla MR scanners (Discovery MR750, GE Healthcare), using a 5-minute 3D sagittal qDESS scan with an 8-channel transmit-receive knee coil (InVivo). qDESS generates two echoes per repetition time: S+ (with T_1/T_2 contrast; echo time (TE) 5.7 ms; Figure 1a), and S- (with T_2 weighting; TE 30.1 ms; Figure 1b) [16]. The sagittal qDESS images were used to generate axial and coronal reformats (Figure 1d-f). Sequence parameters of qDESS are described in Table 2.

Table 2. qDESS MRI sequence parameters

Sequence	qDESS
Matrix (RO × PE)	416×512
In-plane Resolution (mm2)	0.42×0.31
Slice Thickness (mm)	1.5
Number of Slices	80
TE S+, TE S- (ms)	5.7, 30.1
Number of Echoes	2
TR (ms)	17.9
Flip Angle (°)	20
Bandwidth (± kHz)	42
Parallel Imaging	2x1
% Corners Cut	25
Scan Time (mm:ss)	04:48

Abbreviations: qDESS = quantitative double-echo steady-state; MRI = magnetic resonance imaging; RO = readout; PE = phase encodes; TE = echo time; TR = repetition time

Structural analysis of knee OA (MOAKS scoring)

Structural, semi-quantitative assessment of cartilage and meniscus was performed using MOAKS [11] by the same researcher (SE). Both qDESS echoes with multiplanar reformatting

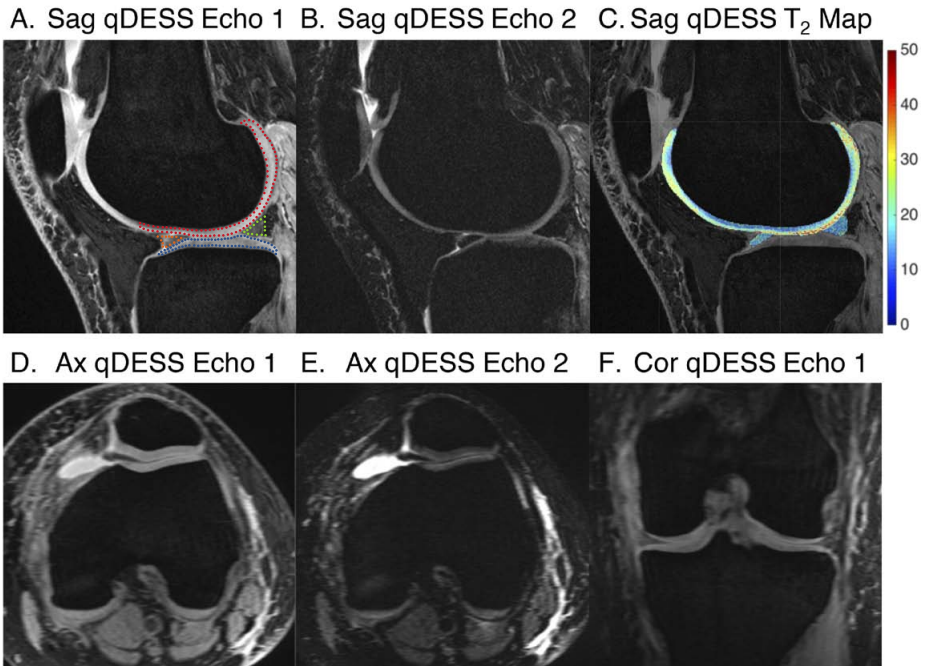

Figure 1. Representative example of (a) first and (b) second sagittal qDESS echo in 37-year-old female without OA, lateral compartment. In (a), femoral cartilage ROI is indicated by red dots, tibial cartilage ROI is indicated by blue dots, anterior meniscal horn is indicated by orange dots and posterior meniscal horn is indicated by green dots. (c) Corresponding T_2 colormaps of femoral cartilage and the anterior and posterior horn of the lateral meniscus (color bar on the right shows the range of T_2 values). Sagittal qDESS images are used to generate reformatted reconstructions in the (d, e) axial and (f) coronal plane. Abbreviations: Sag = sagittal; Ax = axial; Cor = coronal.

were used. Criteria for MOAKS grading for cartilage ($MOAKS_{cartilage}$) and meniscus ($MOAKS_{meniscus}$), used in this study, are described in Supplementary Material 1 and 2, respectively. We performed no second reading because high intra- and inter-observer reproducibility for MOAKS scoring using qDESS with separated echoes, especially for cartilage and meniscus, was reported in a previous study [16].

Quantitative MR analysis

The two echoes of qDESS were used to compute T_2 relaxation time parameter maps, by inverting the qDESS signal model [24]. qDESS T_2 measurements have shown to have high concordance with multi-echo spin echo T_2 measurements [25] and limited sensitivity to T_1 and signal to noise ratio variations in cartilage and meniscus [26]. The first echo (S+) of sagittal qDESS was used for manual segmentation of cartilage and menisci for the calculation of T_2 relaxation times (Figure 1c). Segmentation was performed on single slices, by the same researcher (SE) blinded for the patient's clinical data. For femoral and tibial cartilage segmentation, the centermost

slice through the medial and lateral femoral condyle (defined as the slice midway between the slice on which the femoral condyle was first visible and the slice on which the femoral condyle was last visible) was identified. Four cartilage regions of interest (ROIs) were defined per patient: medial and lateral femoral cartilage as well as medial and lateral tibial cartilage. The trochlear cartilage was not included in quantitative analysis because of the potential influence of the magic angle effect on T_2 relaxation times in that specific region [27].

For meniscus segmentation, the sagittal slice depicting the maximum dimension of the anterior horn and posterior horn as individual triangles was used. Four meniscus ROIs were defined per patient: the anterior and posterior horn of the medial and lateral menisci. To avoid partial volume effects of joint fluid in case of a meniscal tear, the torn area was not included in segmentation. All segmentations and subsequent T_2 analyses were performed using custom in-house software created in MATLAB (version R2011b; The Math-Works).

Statistical analysis

We assessed the intra- and interobserver reproducibility for KLG scoring by calculating weighted Cohen's kappa's. Tests for normality of baseline characteristics and outcomes were performed using Shapiro-Wilk tests. Between-group differences in overall (i.e., pooled across all ROIs) T_2 values and MOAKS scores were evaluated using ANOVA (for parametric data) or Kruskal-Wallis tests (for non-parametric data). In case of statistically significant differences in mean age and/or sex among the three subject groups, a multivariate model with linear regression was used to assess the potential influence of these differences on T_2 values and MOAKS scores. Associations between radiographic OA and T_2 values and between radiographic OA and MOAKS were assessed in predefined cartilage and meniscus ROIs, and for overall scores using correlation analysis for ordinal variables (Spearman's correlation). Differences were considered statistically significant at $P < 0.05$. All statistical analyses were performed using SPSS (version 24.0.0.0, 2018).

RESULTS

Characteristics of study population

Out of the 196 potentially eligible patients, 53 subjects were included in this study: 20 subjects without knee OA, 18 subjects with mild knee OA, and 15 subjects with moderate knee OA. A flowchart of the selection of the study population is presented in Figure 2. Characteristics of study participants, stratified by degree of OA, are summarized in Table 3. There was a slight overall male predominance of 60%, yet no statistically significant differences in sex distribution were found across the three subject groups. The mean age of patients with mild and moderate OA was statistically significantly higher ($P < 0.001$) compared to subjects

with no OA. No statistically significant association between age and T_2 values or MOAKS scores was found (data not shown).

Reproducibility of KLG scoring

Interobserver reproducibility for scoring the degree of radiographic knee OA according to KLG was good (weighted kappa: 0.78), while intra-observer reproducibility was excellent (weighted kappa: 0.85).

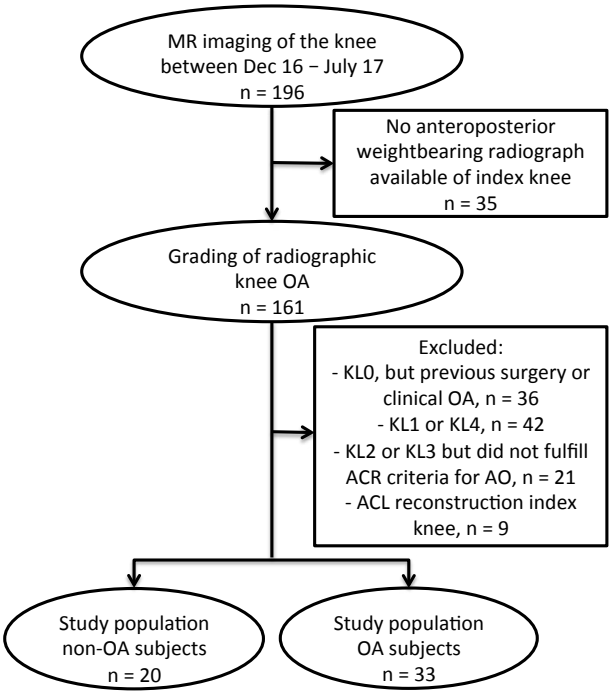

Figure 2. Flow-chart showing the selection process of the study population. In the rectangles on the right, the number and nature of exclusions is described. Abbreviations: MR = magnetic resonance; Dec = December; OA = osteoarthritis; KL = Kellgren and Lawrence grade; ACR = American College of Rheumatology; ACL = anterior cruciate ligament.

qDESS T_2 and MOAKS measurements in cartilage

Overall qDESS cartilage (i.e., pooled across all ROIs) T_2 values were 36.1 ± SD 4.3, 40.6 ± 5.9 and 47.1 ± 4.3 ms for no, mild, and moderate OA, respectively. The delta value (difference) in T_2 was 4.6 ms between no OA and mild OA and 6.5 ms between mild OA and moderate OA. Overall qDESS cartilage T_2 values were similar to T_2 values in previous literature (33.8-38.8, 34.9-41.8 and 40.5-46.9 ms for no, mild, and moderate OA, respectively [7,16,28]). Differences in qDESS T_2 values were statistically significant between the three subject groups ($P < 0.01$, Figure 3a).

Table 3. Characteristics of the study population			
	No Knee OA	Mild Knee OA	Moderate Knee OA
All patients			
No. of patients	20	18	15
Age (y)[a]	34 ± 13	53 ± 13	59 ± 17
Female patients			
No. of patients	7 (35%)	6 (34%)	8 (53%)
Age (y)[a]*	38 ± 14	51 ± 14	62 ± 14
Male patients			
No. of patients	13 (65%)	12 (66%)	7 (47%)
Age (y)[a]*	32 ± 12	53 ± 14	54 ± 21

a: Mean values ± standard deviation

* There were statistically significant differences (P < 0.001) in age between the three subject groups

Abbreviations: OA = osteoarthritis; y = years

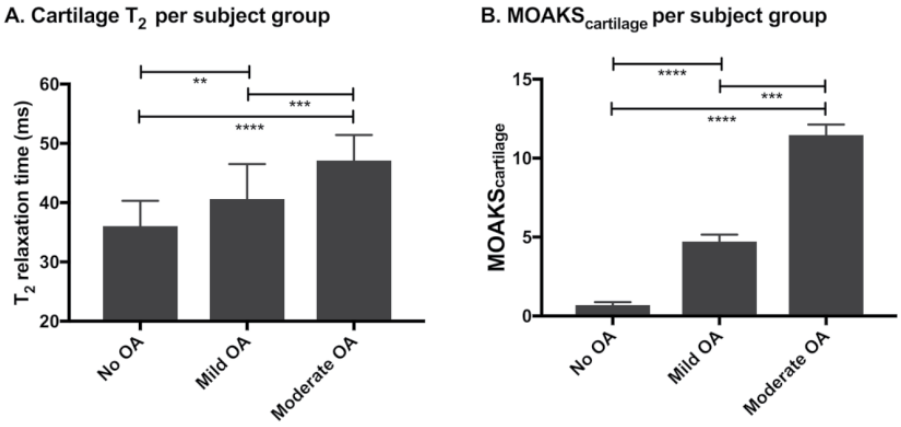

Figure 3. Discriminative power of quantitative and structural qDESS-based measurements in cartilage. Statistical significantly differences in (a) cartilage T_2 and (b) $MOAKS_{cartilage}$ scores were found among subject groups. Data is shown as overall mean values (pooled across all ROIs); vertical bars represent standard deviation. Horizontal bars represent statistically significance between two subject groups; ** = P < 0.01, *** = P < 0.001, **** = P < 0.0001. Abbreviations: ms = milliseconds; OA = osteoarthritis; ROI = region of interest.

Table 4. Cartilage T_2 values and MOAKS$_{cartilage}$ scores per ROI and overall scores, and their correlation with radiographic degree of OA

	No OA		Mild OA		Moderate OA		Correlation with radiographic OA[a]	
	T_2[b]	MOAKS$_{cartilage}$	T_2[b]	MOAKS$_{cartilage}$	T_2[b]	MOAKS$_{cartilage}$	T_2[b] vs. KLG	MOAKS vs. KLG
Cartilage ROI:	*Mean ± SD*	*Mean ± SD*	*Mean ± SD*	*Mean ± SD*	*Mean ± SD*	*Mean ± SD*	*Rho (95%-CI)*	*Rho (95%-CI)*
Medial femur	36.5 ± 5.0	0.4 ± 0.7	43.4 ± 6.1	1.7 ± 1.5	50.6 ± 7.2	3.5 ± 2.9	0.71 (0.53-0.82)	0.62 (0.42-0.77)
Lateral femur	37.2 ± 4.4	0.3 ± 0.7	40.8 ± 5.4	1.3 ± 1.2	48.8 ± 8.4	2.4 ± 2.7	0.57 (0.35-0.73)	0.50 (0.26-0.69)
Medial tibia	34.7 ± 3.7	0.1 ± 0.2	39.4 ± 5.8	1.1 ± 2.4	44.2 ± 6.7	3.4 ± 3.7	0.53 (0.30-0.71)	0.51 (0.28-0.69)
Lateral tibia	35.8 ± 5.0	0.0 ± 0.0	38.8 ± 6.3	0.6 ± 1.2	44.8 ± 8.6	2.2 ± 2.8	0.43 (0.17-0.63)	0.51 (0.28-0.69)
Cartilage overall[c]	36.0 ± 4.3	0.7 ± 0.2	40.6 ± 5.9	4.7 ± 0.4	47.1 ± 4.3	11.5 ± 0.7	0.75 (0.60-0.85)	0.82 (0.70-0.89)

a: Data is shown as Spearman's Rho correlation coefficient between KLG and corresponding T_2 or MOAKS score, with 95% confidence interval shown between brackets
b: In milliseconds (ms)
c: Pooled across all ROIs
Abbreviations: ROI = region of interest, KLG = Kellgren Lawrence grade, OA = osteoarthritis, SD = standard deviation, 95%-CI = 95% confidence interval

Likewise, overall $MOAKS_{cartilage}$ scores were consistently higher with increasing stages of OA with statistically significant differences found between the three subject groups ($P < 0.001$; Figure 3b). The delta value (difference) in $MOAKS_{cartilage}$ was 4 between no OA and mild OA and 6.8 between mild OA and moderate OA. A representative example of qDESS $MOAKS_{cartilage}$ findings in a subject with moderate OA, compared to a corresponding fat-suppressed T_2-weighted image, is provided in Figure 4. Osteophytes were not included in the analyses of the present study, but they were identified on qDESS images. Subchondral cysts and surrounding bone marrow lesions (BMLs) were not included in the analyses of this study but identified as well (see Figure 4). Overall qDESS T_2 and MOAKS scores for cartilage, stratified by degree of OA, are summarized in Table 4.

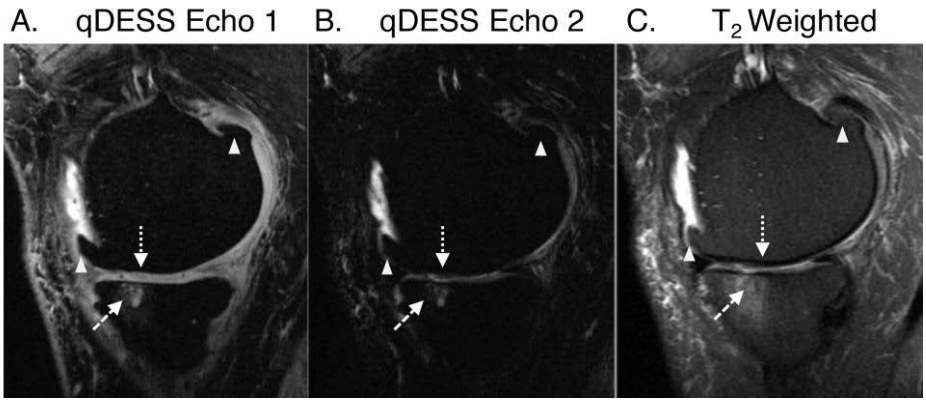

Figure 4. Example of $MOAKS_{cartilage}$ assessment in 71-year-old male with moderate OA on (a, b) qDESS images, compared to (c) corresponding fat-suppressed T_2-weighted image (TE 54 ms; flip angle 142°; FOV 14 cm; matrix 384x192). Sagittal images of (a) first and (b) second qDESS echo show thinning of medial femoral cartilage (dotted arrow). Subchondral cysts and surrounding BML (dashed arrow) and osteophytes (triangles) were not included in the analysis of the present study, but they were identified on qDESS images. Note the underestimation of BML size on qDESS images compared to T_2-weighted image. Abbreviations: OA = osteoarthritis; BML = bone marrow lesion.

qDESS T_2 and MOAKS measurements in menisci

In menisci, overall (i.e., pooled across all ROIs) qDESS T_2 values were 15 ± SD 3.6, 17.5 ± 3.8 and 20.6 ± 4.7 ms for no, mild, and moderate OA, respectively. The delta value (difference) in T_2 was 2.5 ms between no OA and mild OA and 3.1 ms between mild OA and moderate OA. Overall qDESS meniscus T_2 values were similar to T_2 values in previous studies (11.4-21.3, 13.5-22.4 and 16.8-24.2 ms for no, mild, and moderate OA, respectively [7,16,29]). Differences in qDESS T_2 values were statistically significant between the three subject groups ($P < 0.01$; Figure 5a).

Differences in qDESS $MOAKS_{meniscus}$ scores were statistically significant between the three subject groups ($P < 0.001$; Figure 5b), except for the difference in $MOAKS_{meniscus}$ scores be-

tween subjects with mild and moderate OA. The delta value (difference) in $MOAKS_{meniscus}$ was 2.2 between no OA and mild OA and 1.5 between mild OA and moderate OA. An example of qDESS $MOAKS_{meniscus}$ assessment in a subject with mild OA, compared to a corresponding proton density-weighted image, is provided in Figure S1. Overall qDESS T_2 values and MOAKS scores for menisci, stratified by degree of OA, are summarized in Table 5.

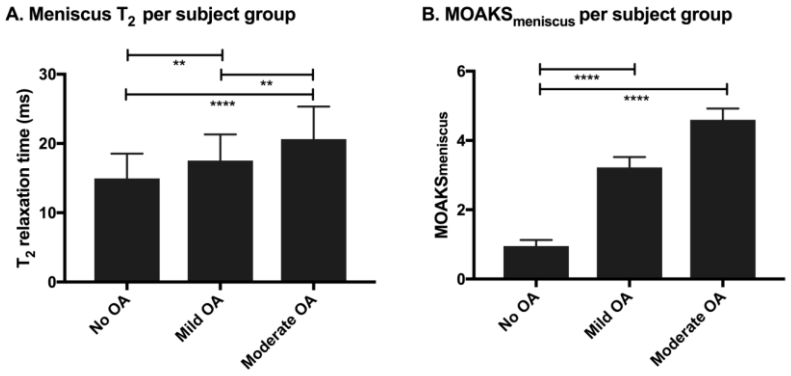

Figure 5. Discriminative power of quantitative and structural qDESS-based measurements in menisci. Statistical significantly differences in (a) meniscus T_2 and (b) $MOAKS_{meniscus}$ scores were found among subject groups. Data is shown as overall mean values (pooled across all ROIs); vertical bars represent standard deviation. Horizontal bars represent statistically significance between two subject groups; ** = P < 0.01, *** = P < 0.001, **** = P < 0.0001. Abbreviations: ms = millisecond; OA = osteoarthritis; ROI = region of interest.

With regard to meniscus extrusion, the presence of meniscus extrusion was consistent with the degree of OA. We found a medial extrusion of 0.3 ± SD 0.1, 0.9 ± 0.3 and 1.1 ± 0.3 in non-OA subjects, subjects with mild OA, and subjects with moderate OA, respectively. A lateral extrusion of 0.0 ± SD 0.0, 0.4 ± 0.2 and 0.7 ± 0.3 was found in non-OA subjects, subjects with mild OA, and subjects with moderate OA, respectively. Statistically significant differences in medial and lateral extrusion grade were found among the three subject groups (P = 0.04 and P = 0.03 for medial and lateral extrusion, respectively).

qDESS T_2 and MOAKS in cartilage and meniscal ROIs

qDESS T_2 values and MOAKS scores for each cartilage and meniscus ROI, stratified by degree of OA, are summarized in Table 4 and Table 5, respectively. In all cartilage and meniscus ROIs, statistically significant correlations were found between qDESS T_2 values and radiographic OA and between MOAKS scores and radiographic OA. The strongest correlation (r = 0.71) between MRI findings and radiographic OA was found in the medial femoral cartilage, the weakest correlation (r = 0.29) was found in the anterior horn of the medial meniscus.

Table 5. Meniscus T_2 values and MOAKS$_{meniscus}$ scores per ROI and overall scores, and their correlation with radiographic degree of OA

	No OA		Mild OA		Moderate OA		Correlation with radiographic OA[a]	
	T_2[b]	MOAKS$_{meniscus}$	T_2[b]	MOAKS$_{meniscus}$	T_2[b]	MOAKS$_{meniscus}$	T_2[b] vs. KLG	MOAKS vs. KLG
Meniscus ROI:	*Mean ± SD*	*Mean ± SD*	*Mean ± SD*	*Mean ± SD*	*Mean ± SD*	*Mean ± SD*	*Rho (95%-CI)*	*Rho (95%-CI)*
Medial anterior	14.2 ± 2.4	0.1 ± 0.4	16.1 ± 2.5	0.4 ± 1.1	17.7 ± 5.2	0.7 ± 1.2	0.39 (0.13-0.60)	0.29 (0.02-0.53)
Medial posterior	16.3 ± 5.9	0.5 ± 0.9	19.6 ± 4.8	1.1 ± 1.2	22.9 ± 7.6	1.3 ± 1.2	0.50 (0.25-0.68)	0.34 (0.07-0.57)
Lateral anterior	14.8 ± 3.5	0.2 ± 0.7	17.2 ± 3.8	1.1 ± 1.0	20.6 ± 5.3	1.3 ± 1.5	0.51 (0.27-0.69)	0.45 (0.19-0.65)
Lateral posterior	14.6 ± 2.4	0.2 ± 0.7	17.2 ± 4.0	0.7 ± 1.0	21.2 ± 7.9	1.3 ± 1.0	0.48 (0.23-0.67)	0.52 (0.29-0.70)
Meniscus overall[c]	15.0 ± 3.6	1.0 ± 0.2	17.5 ± 3.8	3.2 ± 0.3	20.6 ± 4.7	4.6 ± 0.3	0.64 (0.44-0.78)	0.65 (0.45-0.79)

a: Data is shown as Spearman's Rho correlation coefficient between KLG and corresponding T_2 or MOAKS score, with 95% confidence interval shown between brackets
b: In milliseconds (ms)
c: Pooled across all ROIs
Abbreviations: ROI = region of interest, KLG = Kellgren Lawrence grade, OA = osteoarthritis, SD = standard deviation, 95%-CI = 95% confidence interval

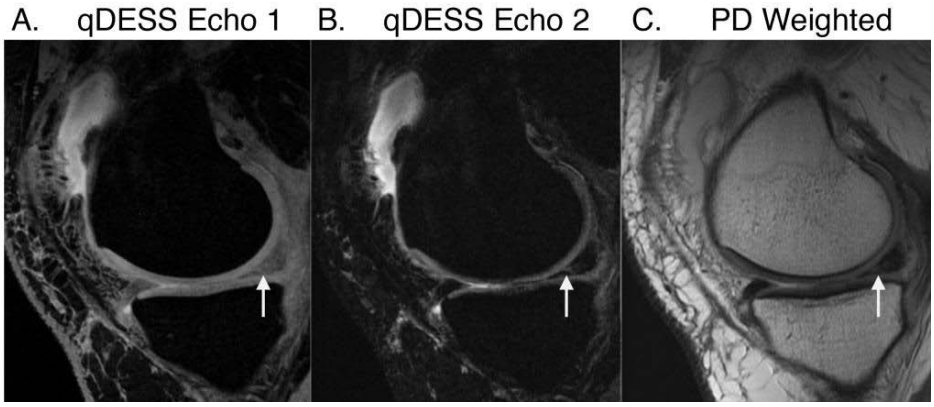

Figure S1. Example of $MOAKS_{meniscus}$ findings in 47-year-old male with mild OA, on sagittal images of (a) first and (b) second qDESS echo, compared to (c) corresponding proton density-weighted image (TE 35 ms; flip angle 142°; FOV 14 cm; matrix 384x224), showing a complex tear (solid arrow) in the posterior horn of the medial meniscus. $MOAKS_{meniscus}$ scoring in the present study included meniscus signal, tears, and (partial) maceration. The second qDESS echo especially was useful in identifying meniscus pathology. Abbreviations: OA = osteoarthritis; PD = proton density.

DISCUSSION

In the present study, we demonstrated that quantitative and structural measurements in cartilage and meniscus, obtained with a single 5-minute qDESS sequence, can differentiate between OA stages. T_2 values in cartilage and menisci were similar to T_2 values reported in previous studies [5-8].

The disease distribution of OA within the knee joint is often compartmental, with high variability regarding compartmental involvement [6,20,21]. Therefore, we assessed the validity of qDESS-based biomarkers in various cartilage and meniscus ROIs. The discriminative power to distinguish degree of OA was the greatest in the medial femoral cartilage, and the least in the anterior horn of the medial meniscus. These findings were most likely caused by the uneven distribution of OA features; the anterior horn of the medial meniscus showed relatively low T_2 values and MOAKS scores in subjects with mild or moderate OA while the medial femoral cartilage showed relatively high T_2 values and MOAKS scores in those subjects. Despite the differences in discriminative power, T_2 values and MOAKS outcomes in all ROIs were found to be statistical significantly correlated with radiographic knee OA.

The qDESS sequence in the present study was optimized to simultaneously generate high resolution images and quantitative measurements, by combining high spatial resolution with high SNR, in one single, rapid scan. While twice as fast, the resolution and voxel volume of this qDESS sequence (0.18μL) was over 10x better than the resolution of established quantitative T_2 sequences [7,30]. In a previous study, qDESS has shown high T_2 accuracy compared to multi-echo spin echo sequences, as well as high accuracy for MOAKS measurements

compared to conventional spin echo based sequences, with high intra- and inter-observer reproducibility [16,25]. qDESS has been thought to underestimate the size of bone marrow lesions (BMLs), which seems to be the case in our study as well (see Figure 4, not studied), likely due to T_2* susceptibility effects [15]. A separation of the two qDESS echoes may enhance accuracy of BML detection compared to previous qDESS studies [31]. Although outside the scope of this study, further work is needed to test and optimize BML detection with qDESS.

Building upon the work of Chaudhari et al. [16], the present study assesses the discriminative power of a 5-minute qDESS sequence to obtain T_2 values and MOAKS in a clinical knee OA population. We validated T_2 measurements and MOAKS against radiographic OA, which remains the gold imaging standard for diagnosing and monitoring knee OA [18,19]. In OA research, KLG2 is considered the cut-off point for the presence of radiographic knee OA [4,18,19,32]. Although potentially a relevant group in the context of early OA imaging, we did not include patients with KLG1, indicating doubtful radiographic OA. The reproducibility of scoring KLG1 (i.e., doubtful narrowing of joint space and possible osteophytic lipping) is relatively poor, most likely due to differences in the interpretation of radiographic findings, especially concerning osteophytic lipping [18]. Also, patients with severe radiographic OA (i.e. KLG4) were not included in the present study, as bony deformity and bone-to-bone contact precludes accurate segmentation of cartilage.

OA is among the top ten burdensome diseases, with the knee being the most affected joint [1]. In the light of increased numbers associated MR imaging studies [2,33], reducing MR imaging acquisition time is highly relevant. Reducing scan time saves costs and increases patient comfort and may reduce motion artifacts in longer acquisitions [16]. Because qDESS rapidly provides rich structural and quantitative information, there is a great promise for using this technique in large clinical OA studies. Recent advances in deep learning and simultaneously imaging both knees with qDESS may further reduce scan time, without loss of image quality or quantitative accuracy [34-36].

This study has some limitations that must be acknowledged. First, segmentation of quantitative analysis and MOAKS scoring was performed by a single, experienced researcher. As evidence of high intra- and inter-observer reproducibility for cartilage and meniscus segmentation and MOAKS assessment with qDESS images has been reported previously [16], analyses performed by a single researcher was considered sufficient. Second, our validation study was cross-sectional. The lack of a longitudinal aspect may limit interpretation regarding the potential use of qDESS in clinical trials. Therefore, future studies on the sensitivity of qDESS-based biomarkers for longitudinal changes in the knee are required. Third, KLG was used as reference standard, which is considered the gold standard for imaging-based knee OA classification [4]. Radiographically detected joint space narrowing (JSN) is currently the only structural endpoint accepted by the European and US regulatory bodies (European Medicines Agency and FDA) to assess knee OA progression [37] and is commonly used in qMRI

validation studies [6,7]. We opted for this method because we aimed to explicitly use qDESS in a clinically relevant matter. However, an important drawback of the KLG method is the low reproducibility of JSN measures reported in literature, in particular in longitudinal assessment of knee OA [4,38]. Given the cross-sectional design of our study without longitudinal measures, challenges concerning longitudinal KLG measures are unlikely. To optimize reproducibility, we used standardized radiographs (weight-bearing AP). To assess reproducibility, both inter- and intra-observer reproducibility of KLG were carefully evaluated in the present study (weighted kappa of 0.78 and 0.85 for inter- and intra-observer reproducibility respectively). Finally, although osteophytes and BMLs are important OA features, they were not studied. The primary objective of this study was to assess the validity of qDESS for cartilage and menisci in OA subjects. We focused on those tissues as they have conclusively been shown to be strong indicators for OA and because of their possibilities in both quantitative (T_2) and semi-quantitative (MOAKS) [4,7,8,11,39]. To assess the external validity of our study results, further studies evaluating other relevant OA features will be essential, in particular regarding BML detection. In addition, future validation studies on qDESS T2 values in OA patients against histological degree of degeneration (the gold standard for tissue changes) are desirable.

In conclusion, quantitative T_2 and structural assessment of cartilage and meniscus with a single 5-minute qDESS scan can distinguish between different grades of OA and show significant correlations with the reference standard. These results demonstrate the potential of qDESS as an efficient and accurate imaging tool for OA research.

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SUPPLEMENTARY MATERIAL 1: MOAKS GRADING FOR CARTILAGE

For structural, semi-quantitative assessment of cartilage in the present study, cartilage subscores ($MOAKS_{cartilage}$), directly derived from the MOAKS total scores, were used (described in Table S1). $MOAKS_{cartilage}$ includes the size of cartilage lesions and the percentage of cartilage lesions being full thickness [1].

Table S1. MOAKS grading for cartilage

Findings on MR images	MOAKS score for % full thickness	MOAKS score for size of cartilage lesions	MOAKS cartilage score[a]
Normal	0	0	0
1–10% of the cartilage area damaged No full-thickness cartilage loss	0	1	1
1–10% of the cartilage area damaged 1–10% full-thickness cartilage loss	1	1	2
10-75% of the cartilage area damaged No full-thickness cartilage loss	0	2	2
10-75% of the cartilage area damaged 1-10% full-thickness cartilage loss	1	2	3
10-75% of the cartilage area damaged 10-75% full-thickness cartilage loss	2	2	4
>75% of the cartilage area damaged No full-thickness cartilage loss	0	3	3
>75% of the cartilage area damaged 1-10% full-thickness cartilage loss	1	3	4
>75% of the cartilage area damaged 10-75% full-thickness cartilage loss	2	3	5
>75% of the cartilage area damaged >75% full-thickness cartilage loss	3	3	6

a: MOAKScartilage score is the sum of MOAKS score for % full thickness and MOAKS score for size of cartilage lesions
Abbreviations: MR = magnetic resonance

SUPPLEMENTARY MATERIAL 2: MOAKS GRADING FOR MENISCUS

For structural, semi-quantitative assessment of the meniscus in the present study, meniscus subscores ($MOAKS_{meniscus}$) based on MOAKS total scores were used, including meniscus signal, tears, and (partial) maceration (described in Table S2). The rationale behind $MOAKS_{meniscus}$ criteria and the hierarchy in $MOAKS_{meniscus}$ scoring used in the present study was based on the clinical important effects these meniscus findings have as described in literature [2; 3]

Table S2. MOAKS grading for meniscus

Findings on MR images	**MOAKSmeniscus score**
Normal meniscus	0
Signal	1
Non-complex tear and/or meniscal cyst	2
Complex tear and/or partial maceration	3
Complete maceration	4
Extrusion findings on MR images[a]	**MOAKS extrusion score**
< 2 mm	0
2-2.9 mm	1
3-4.9 mm	2
> 5 mm	3

a: Measured on coronal image, excluding osteophytes
Abbreviations: MR = magnetic resonance

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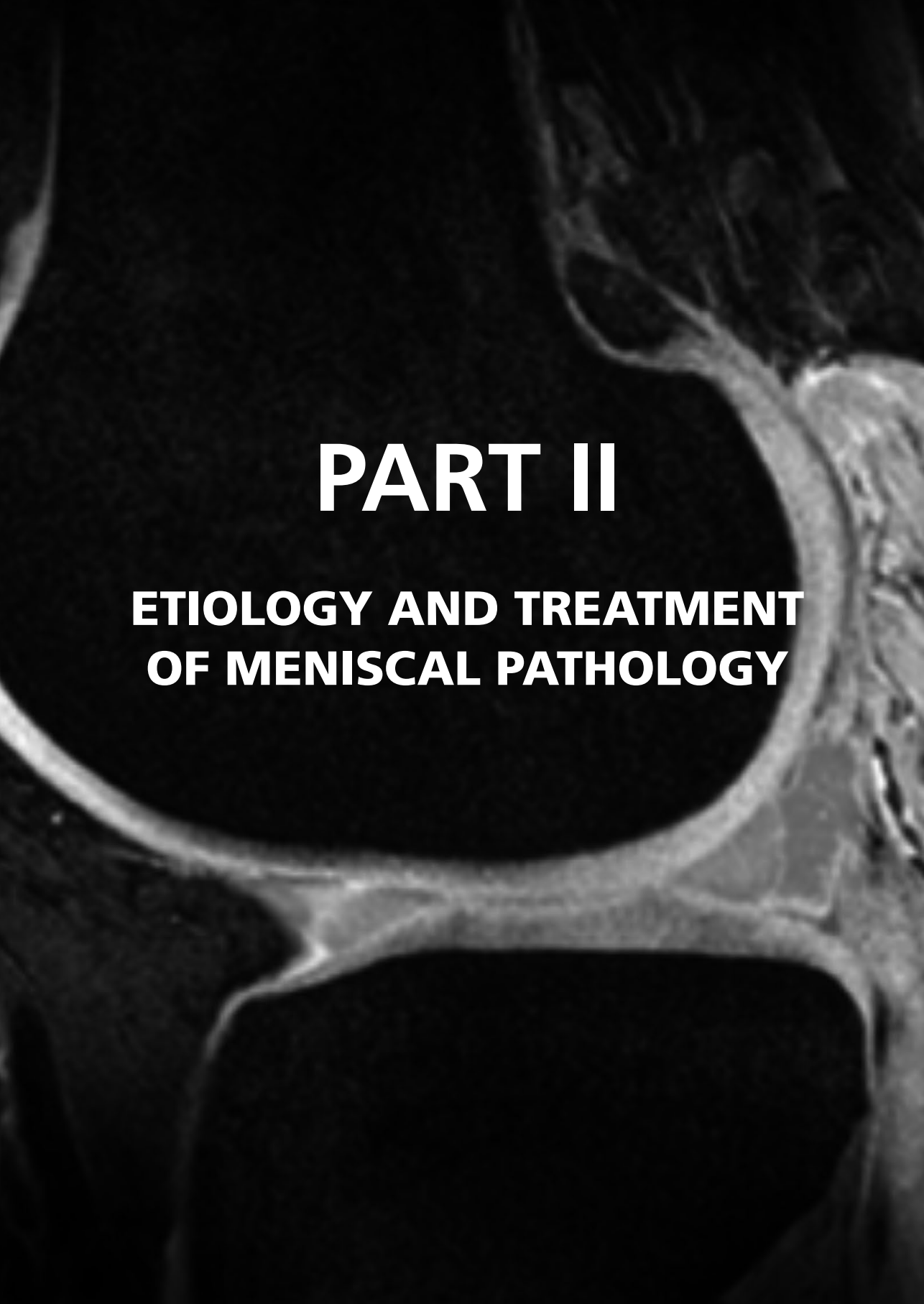
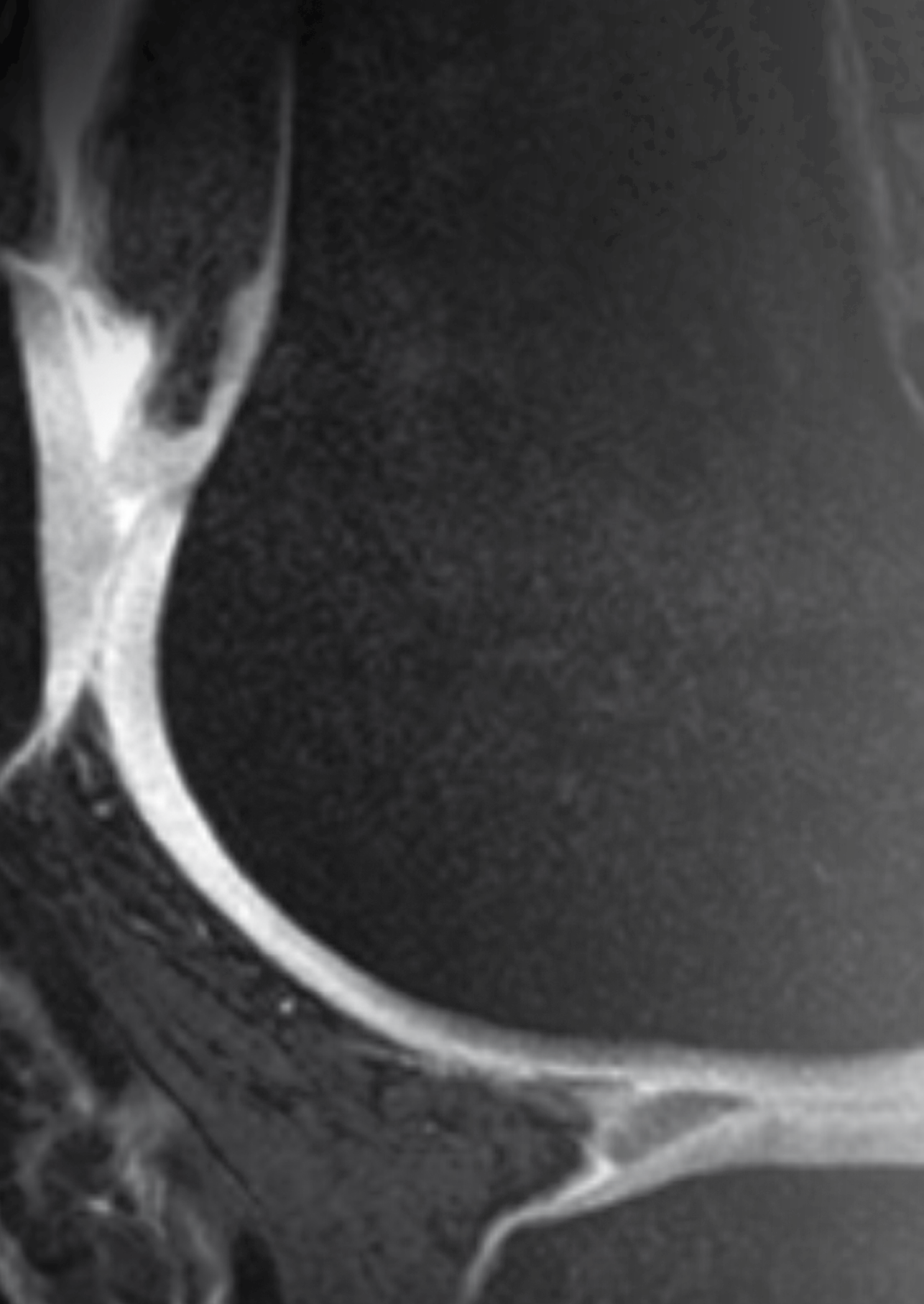


PART II

ETIOLOGY AND TREATMENT OF MENISCAL PATHOLOGY



Chapter 5

Meniscal extrusion and degeneration during the course of osteoarthritis in the murine collagenase-induced osteoarthritis model

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ABSTRACT

Objective: Meniscal damage is, despite its major role in knee osteoarthritis (OA), often neglected in OA animal models. We evaluated structural meniscal degeneration during the course of OA in the murine collagenase-induced OA (CIOA) model.

Methods: OA was induced in the knee joints of 33 male C57BL/6 mice by an intra-articular injection of 10U collagenase. The mice were sacrificed after 1, 3, 7, 14, 28, and 56 days, and the knees were harvested and processed for histological analysis. As control, 6 knees were obtained from 16-week-old mice in which no OA was induced. Meniscal damage, meniscal extrusion, and articular cartilage damage were evaluated on thionin-stained sections. Associations between parameters of interest were evaluated with Spearman rho correlation tests.

Results: When compared to non-OA knees, meniscal extrusion was visible from day one onwards and meniscal degeneration had a tendency to increase over time. The meniscus damage appeared around the same time as articular cartilage damage (day 14-28) and was statistically significantly more pronounced anterior than posterior, and no differences were seen between medial and lateral menisci. Meniscus and articular cartilage damage were moderately associated in the CIOA knees (ρ=0.57; 95%CI [0.23-0.78]).

Conclusions: Our findings suggest that the CIOA model is a valuable model to study the role of meniscal damage during OA progression and can support the development of future preventative treatment strategies.

INTRODUCTION

Meniscal degradation is, in spite of its critical role in knee osteoarthritis (OA), often neglected in OA animal models. Meniscal damage is one of the strongest identified risk factors for the development and progression of knee OA [1-7]. In addition, indications that meniscal extrusion, that is, radial displacement of the meniscus outside of the joint cartilage margin, is independently related to knee OA development have been reported previously [8-10]. Meniscal integrity is, therefore, an important factor in the long-term health of the knee joint [11]. Paradoxically, little is known of the exact relationship between meniscal degradation and cartilage degeneration in the development of knee OA.

Murine models for OA are frequently used to study the etiopathogenesis of knee OA in fundamental and translational studies, due to the possibility to study the disease on a pathophysiological level, or to study the effects of an experimental therapy [12]. Despite its major role in knee OA, the menisci are grossly neglected in the diagnosis of murine knee OA. A frequently used enzyme-based model is the collagenase-induced OA (CIOA) model [13], where highly purified collagenase is injected intra-articularily and affects joint ligaments, resulting in joint instability [13,14]. Another often used murine OA model is the surgical destabilization of the medial meniscus (DMM) [15], a model in which the ligament that attaches the medial meniscus to the tibia is transected, resulting in an instable and displaced meniscus. Recently, a systemic evaluation method for degeneration of the meniscus in experimental OA was established by Kwok et al. [16]. In the study, the authors reported insights on the structural changes of the menisci during ageing and OA and have shown that in the DMM model, meniscal damage and articular cartilage damage develop synchronously from day 14 onwards. No studies have been conducted on the elapsed meniscal degeneration in the CIOA model. Therefore, the aim of this study was to evaluate meniscal damage during the course of experimental knee OA in the CIOA mouse model, immediately after OA onset.

METHODS

Induction of experimental OA

The animal experiments were carried out in correspondence with the ARRIVE Guidelines for Reporting Animal Research [17], and with the approval of the Animal Ethical Committee of the Erasmus Medical Center (approval no. EMC 3246, 114-14-01). OA was induced using the CIOA model in the right knees of 33 male C57BL/6J01aHsd mice (28.4 ± 3.1 g; 12 to 14 weeks old; Envigo, Cambridgeshire, UK) as described previously [13]. Briefly, the mice were randomly taken from their cages and were anesthetized with 3% isoflurane/0.8 L O_2/min (Pharmachemie BV, Haarlem, the Netherlands). The knees were sprayed with 70% ethanol (BoomLab, Meppel, the Netherlands). A dermal incision was then made at the height of the

patellar tendon and a 6 µL solution containing 10U collagenase from *clostridium histolyticum* (Sigma-Aldrich, St. Louise, USA) in saline (Sigma-Aldrich) was injected intra-articularily in the right knees. All animals were housed at the Experimental Animal Facility of the Erasmus Medical Center in standard caging under a standard 12-hour light/dark cycle in groups of 3-9 including cage enrichment and received acid tapwater and standard chow *ad libitum*. The mice were sacrificed by cervical dislocation 1, 3, 7, 14, 28, or 56 days after CIOA induction and the knees were processed for histological analysis. The final number of knees used for analysis was: 8 mice at day 1, 7 mice at day 3, 3 mice at day 7, 9 mice at day 14, 3 mice at day 28, and 3 mice at day 56. As controls, 6 naïve knees were obtained from three 16 week-old mice in which no OA was induced.

Histological scoring of structural meniscal damage, meniscal extrusion, and articular cartilage damage

The knees were harvested and fixed in 4% formaldehyde (BoomLab) for 10 days and decalcified for 10 days in 10% ethylenediaminetetraacetic acid (Sigma-Aldrich). The tissue was then dehydrated in an ascending series of alcohol, embedded in paraffin, and sectioned serially at 6 µm in the coronal plane. The sections were stained with thionin (Sigma-Aldrich) and images were taken with a NanoZoomer 2.0-HT slide scanner (Hamamatsu, Hamamatsu City, Japan).

Meniscal damage was assessed according to the validated method described by Kwok et al.[16] in which the menisci were evaluated based on surface integrity, cellularity and staining intensity, with a maximum possible score of 21. The scoring was separately conducted by two researchers experienced in histological grading (LU and SME) in a complete observation-blinded manner, meaning unaware of time-point, case-control status, and each other's scores. The inter-observer reliability of the meniscus damage scoring was excellent, with an ICC of 0.84 (95%CI [0.63 – 0.93]).

Meniscal extrusion of the medial and lateral meniscal body was assessed on the same sections as used for histological evaluation. Extrusion is where the meniscus is partially or totally displaced from the tibial cartilage surface [9]. This feature was scored from 0 to 4 where: 0=no extrusion, 1 = mild extrusion, 2 = moderate extrusion, 3 = severe extrusion, 4 = complete displacement of the meniscus. The assessment for meniscal extrusion was performed by LU and its evaluation extensively discussed with the co-authors (SME, DM, GJVMvO and YMBJ).

Structural articular cartilage damage was assessed in all four quadrants of the knee in four sections according to a modified grading and staging score for murine cartilage that was initially based on the score described by Pritzker et al. [18]. The score was determined by multiplying a grade (0-6) and a stage (0-4) and the maximum score of four sections of each quadrant was evaluated, accounting for a total of 16 scores throughout the entire knee joint. The score of the four quadrants was then summed to determine the total articular cartilage damage score in the knee resulting in a maximal possible score of 96. The ICC of the cartilage score was 0.81 (95%CI [0.42 – 0.84]).

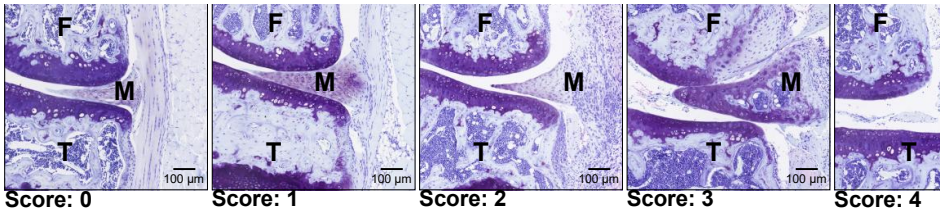
Statistical analysis

Calculations for the histological scores were conducted with MS Excel 2016 (Microsoft, Redmond, USA) and IBM SPSS 23.0 (IBM, New York, USA) was used for statistical evaluation. Mann-Whitney U tests were conducted to evaluate statistically significant differences of the non-parametric values of interests (i.e., meniscus damage and meniscal extrusion) between independent groups (i.e., per time point compared to the non-OA knees). The association between meniscus damage and articular cartilage damage was evaluated with a Spearman rho correlation test followed by Bonferroni correction and bootstrap-based calculations to calculate the 95% confidence interval (95%CI). P values of < 0.05 were considered statistically significant.

RESULTS

Meniscus extrusion and damage during the course of experimental OA

Meniscal extrusion was visible (Figure 1-A) and statistically significantly more present than in the non-OA knees from day 1 onwards (Figure 1-B). No differences in extrusion were seen between the medial and lateral sides (data not shown). Meniscal degeneration was evaluated for surface structure, cellularity, and matrix staining and all three parameters had



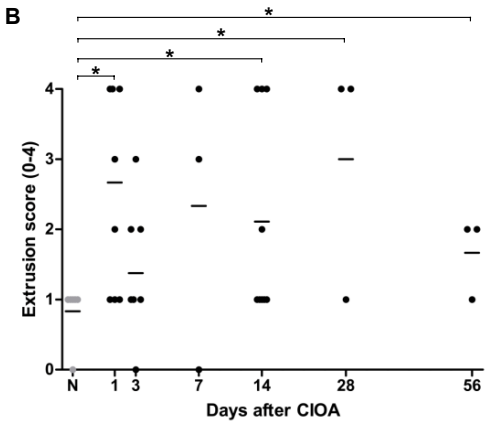


Figure 1. Meniscus extrusion during the course of OA development. A) Representative images of five degrees of meniscal extrusion on thionin-stained sections. B) Meniscal extrusion score after induction of OA where 0 =no extrusion, 1 =mild extrusion, 2 = moderate extrusion, 3 = severe extrusion, 4 = complete displacement of the meniscus. Each symbol represents a data point of the individual knees and the horizontal lines represent the median value. *: $P < 0.05$. Abbreviations: OA = osteoarthritis; F = femural condyle; T = tibia; M = meniscus; M* = displaced meniscus; CIOA = collagenase induced osteoarthritis.

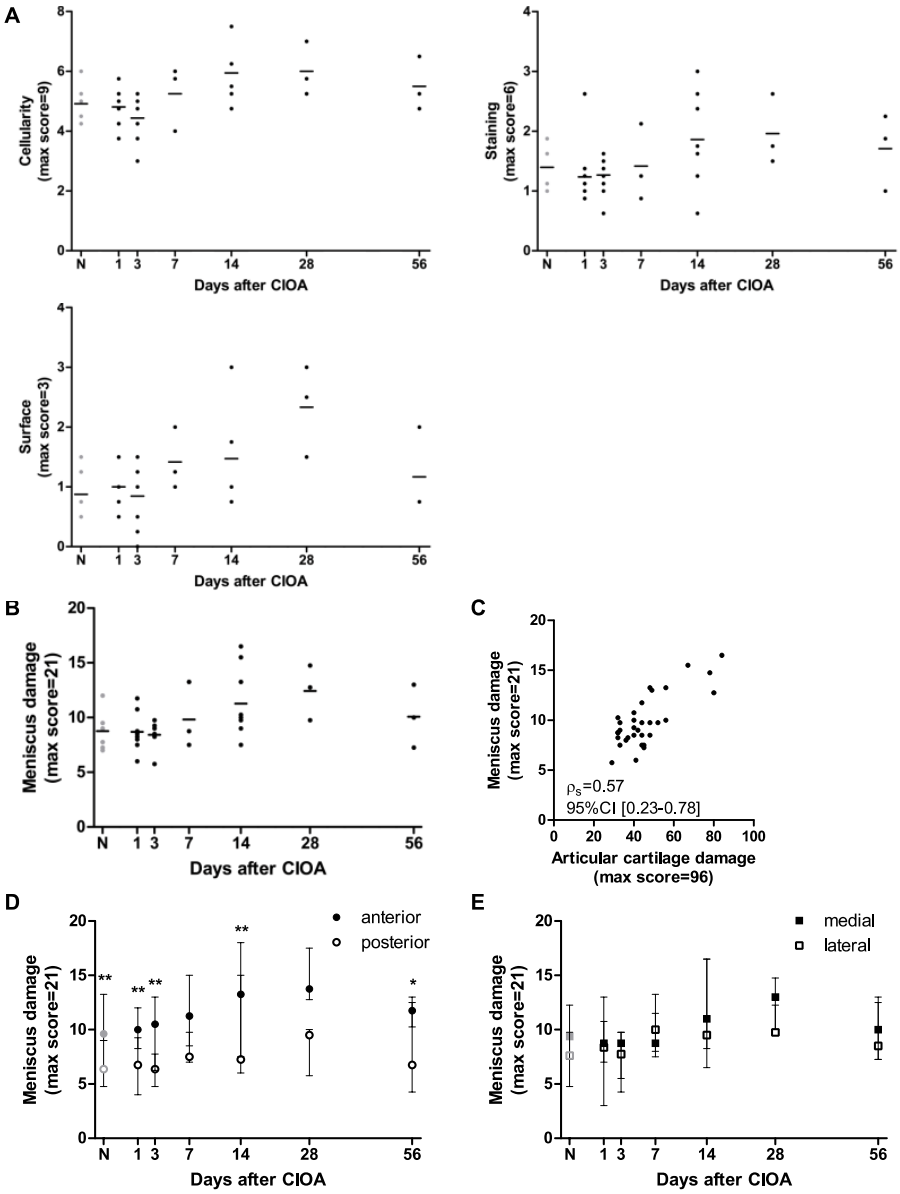


Figure 2: Meniscus damage during the course of collagenase-induced OA in mice knees. A) Subdomains of meniscus damage score; cellularity, staining intensity, surface integrity. Each symbol represents a data point of the individual knees and the horizontal lines represent the median value. B) Plot showing that meniscus damage was mild up until 56 days after induction of OA. Each symbol represents a data point of the individual knees and the horizontal lines represent the median value. C) Spearman correlation between meniscus damage and articular cartilage damage in the CIOA knees. Differences in meniscus damage between (D) anterior and posterior, and (E) medial and lateral sides of the knees. The data is show as median with whiskers from minimum to maximum. *: $P < 0.05$; **: $P < 0.01$. Abbreviations: OA = osteoarthritis; CIOA = collagenase induced osteoarthritis.

a tendency to increase over time compared to the non-OA knees from day 14 on, albeit not significantly (Figure 2-A). When the three parameters were combined, the total meniscus damage score in the CIOA knees tended to be higher at day 14 and 28 than in the non-OA knees (Figure 2-B). Meniscus and articular cartilage damage were moderately associated (ρ=0.57; 95%CI [0.23-0.78]; Figure 2-C) in the CIOA knees and the meniscus damage appeared around the same time as articular cartilage damage (day 14-28; data not shown). As for the locations within the knees where the damage appeared, meniscus degeneration was more pronounced anterior than posterior in both the CIOA knees and non-OA knees (Figure 2--D). No differences were seen between medial and lateral menisci (Figure 2E).

DISCUSSION

We assessed meniscal extrusion and degeneration during the course of OA in the murine CIOA model. The results of this study suggest that structural meniscal degeneration appears simultaneously with articular cartilage degeneration and that they are correlated, indicating that meniscal degeneration is an important parameter when assessing OA in the CIOA model. Despite the fact that the major role of the meniscus in the development of knee OA is well established [1,3-10], this is the first study evaluating meniscal damage in the murine CIOA model. In another study by Kwok *et al*., meniscal degeneration was assessed in the DMM model [16]. As meniscal damage was evaluated only 14 days after OA induction, relevant information during early OA onset may have been missed. In our study, we have found that meniscal damage and cartilage damage appear simultaneously, which is in concordance with findings by Kwok and colleagues [16]. We have additionally shown that meniscal extrusion was higher after one day in the collagenase-injected knees than in the non-OA knees. These findings suggest that the injected collagenase might have also affected the meniscal ligaments that, due to mechanical loading might have become insufficient, leading to meniscus extrusion. The degenerating processes of joint tissues in early stage knee OA is not limited to articular surface cartilage, but also affects meniscus integrity, as suggested in previous literature [6]. Our findings may lead to a deeper understanding of the cascade of the development of knee OA and the complex interplay and role of the meniscus in this context. Ultimately, these insights may contribute to the development of effective therapeutic options for early OA.

Although OA animal models are useful tools to study diseases, they have limitations as well. The CIOA model that is used in this study, can be categorized as a classic model for immediate joint instability and critical structural damage [14,19,20]. Even though the CIOA mouse is a widely used model for knee OA, as it presents with OA characteristics such as structural cartilage damage, osteophytes, synovitis and joint instability, there are obvious important differences between murine and human menisci. The meniscus morphology in mice differs from human menisci; mice menisci are thicker and less symmetrical in the proximal-distal

direction because of the posture of the animal, since a mouse knee is in a more flexed position than a human knee. Moreover, there are differences in histological staining profiles. The staining intensity increases with age and degree of degeneration in human menisci, whereas in mice this is reversed as the staining intensity appears less intense and is disrupted in older subjects [16,21]. The reason for these differences and the meaning for the process of OA development is not clear and must be taken in consideration when assessing meniscal damage in a murine OA model.

CONCLUSION

To conclude, several studies have shown a correlation between extrusion of the meniscal body and knee OA [8,9] and meniscal extrusion is known to be independently related to cartilage loss [8-10,22]. The generally accepted hypothesis is that an extruded meniscus modifies the load distribution and weight-bearing abilities within the knee joint, eventually resulting in the development of knee OA [8,22]. Our study shows that meniscal extrusion appears early in the CIOA mouse model, and that meniscal damage and articular cartilage damage occur simultaneously. This highlights the CIOA model as a valuable model to study the role of meniscal damage during OA progression and the development of future preventative treatment strategies.

Acknowledgements

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Ethical approval

The animal experiments were carried out with the approval of the Animal Ethical Committee of the Erasmus Medical Center, approval no. EMC 3246 (114-14-01).

Conflict of interests

LU, SME, DEM, YMB-J, and GJVMvO have nothing to disclose. SMAB-Z is a consultant for Infirst Healthcare and Regeneron Pharmaceuticals. None of the entities were involved in the design, conduct, or analysis of this study.

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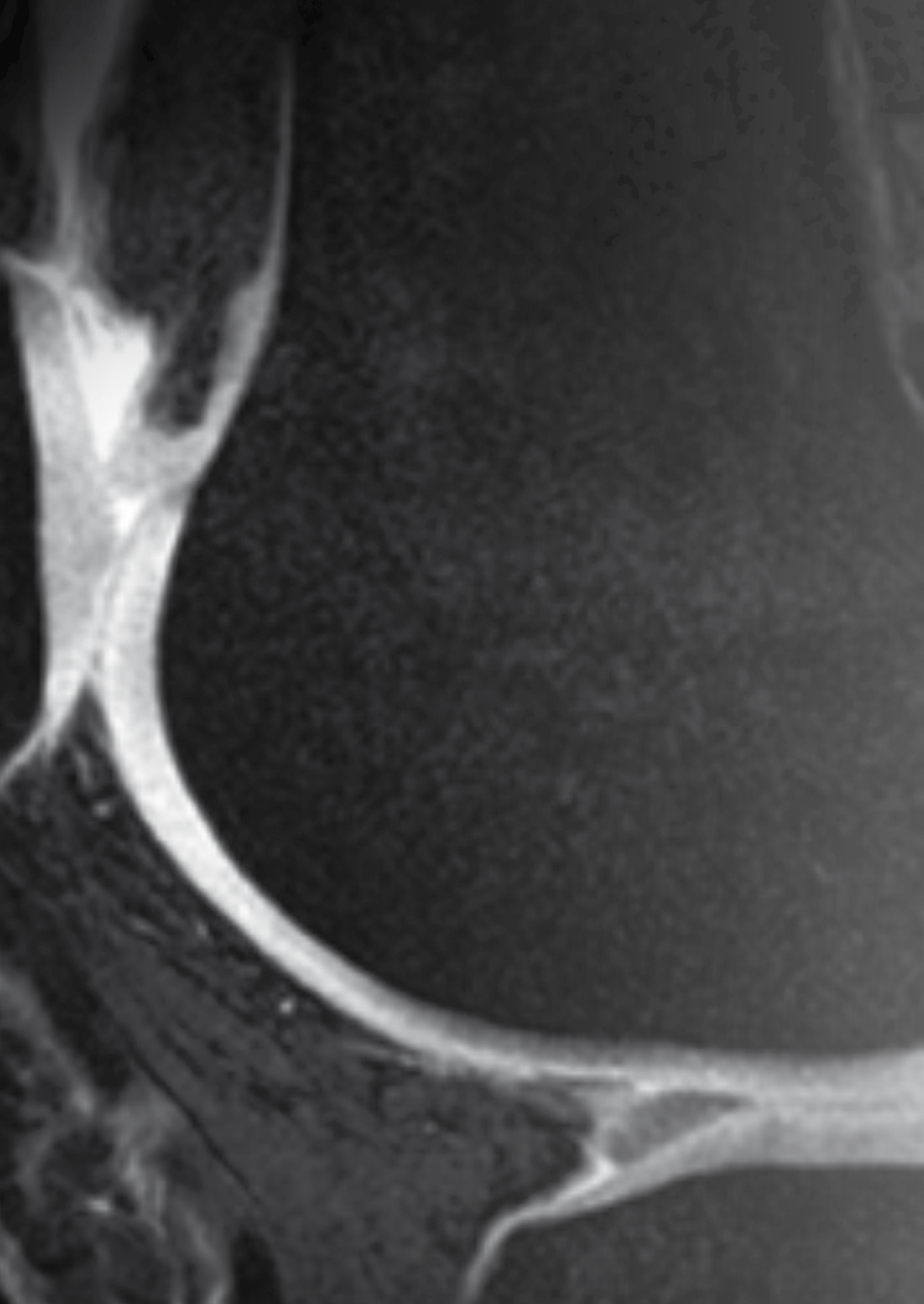

Chapter 6

Traumatic meniscal tears are associated with meniscal degeneration

SM Eijgenraam, MA Wesdorp, DE Meuffels, SMA Bierma-Zeinstra, GJ Kleinrensink, YM Bastiaansen-Jenniskens, M Reijman

Submitted for publication

ABSTRACT

Objective: Meniscal tears are traditionally classified into traumatic versus degenerative tears. Although this classification plays a major role in clinical decision making, no consensus exists on the exact definition of a 'traumatic' or 'degenerative' tear and the histopathological basis for this classification is unclear. Our aim was to assess the histological degree of meniscal degeneration in patients with a traumatic meniscal tear, compared to intact meniscal tissue and to osteoarthritic meniscal tissue.

Methods: Traumatically torn meniscal tissue was collected during arthroscopic partial meniscectomy. As control group, intact meniscal tissue, obtained during trans-femoral amputations or post-mortem dissections, was used. Meniscal tissue from osteoarthritic knees was obtained during total knee replacement surgery. Meniscal tissue was processed, stained, and histologically analyzed using the Pauli scoring system (comprising the subdomains surface integrity, cellularity, collagen organization, and matrix staining). Statistical analysis was performed using ANOVA, univariate and multivariate logistic regression models.

Results: The traumatic meniscal tear group contained 43 patients (34 men, median age 29 year), the intact group eight patients (three men, median age 58 year), and the osteoarthritic group 14 patients (four men, median age 66 year). After adjustment for sex, age, and BMI, patients with a traumatic meniscal tear showed a statistically significantly higher histological score than patients with intact vital meniscal tissue ($P = 0.035$). Histological score between the traumatic and osteoarthritic group was not significantly different. In the traumatic group, the degree of degeneration was not associated with time interval between trauma and surgery.

Conclusion: Traumatically torn menisci showed a higher degree of degeneration than intact menisci. These results may suggest that in patients suffering from a traumatic meniscal tear, a certain degree of meniscal degeneration might already have been present. These findings could potentially challenge the classic view of traumatic versus degenerative meniscal tears.

INTRODUCTION

A symptomatic meniscal tear is the most common knee injury affecting 2 in 1000 patients per year in The Netherlands [1-5]. A torn meniscus can lead to pain, disability and lower quality of life [6]. In the longer term, a meniscal tear is an important risk factor for the development and progression of knee osteoarthritis (OA) [6-8].

Meniscal tears are traditionally classified into traumatic versus degenerative tears, referring to their onset. Currently, this classification is based on medical history, the patient's age, and magnetic resonance imaging (MRI) indicating a specific tear pattern. This classification of meniscal pathology is essential in clinical decision making; traumatic meniscal tears are mostly treated by arthroscopic partial meniscectomy (APM) or repair [9,10], whereas non-operative management is generally the first choice for degenerative tears [10,11]. Classifying meniscal tears into "traumatic" versus "degenerative" tears can, however, be challenging as there is no consensus on how exactly to define degenerative and traumatic tears. In some cases, traumatic tears are caused by a very minor trauma (e.g., walking stairs), and, on the other hand, degenerative tears are incidentally found in asymptomatic ''healthy" knees [12,13]. Moreover, studies have shown that traumatic meniscal tears may result from early degenerative disease processes [14,15]. Thus, differentiation between these two types is not as straight forward as it may seem.

In soft tissues other than the meniscus, the role of tissue condition in pathophysiological processes has been studied before. For instance, degenerative changes were already present in ruptured Achilles tendons [16-20]. These findings have led to the view that degeneration of a tendon can cause it to rupture in absence of an abnormal movement or force; representing the so-called "continuum theory" [21,22]. The continuum theory explains the pathological basis of the heterogeneity between healthy and degenerative tissue eventually leading to tendinopathy or rupture [22]. This rationale might be extended to meniscal tissue. Hence, it is highly relevant to increase knowledge on tissue condition of a torn meniscus. This knowledge could begin to establish a pathophysiologic basis for the classification of meniscal tears. To date, there are no studies published evaluating the degree of histological degeneration in traumatically torn meniscal tissue. Moreover, no research compared traumatically torn to intact meniscal tissue regarding histological degeneration. Histological research so far mainly focused on osteoarthritic and degenerative menisci [23].

Our aim was to investigate the histological degree of degeneration in traumatically torn meniscal tissue, compared to intact vital meniscal tissue as a control group. Osteoarthritic menisci were used as a reference for a degenerative state of the meniscus. Our hypothesis was that traumatically torn meniscal tissue shows a higher degree of histological degeneration compared to intact vital meniscal tissue. A secondary aim was to identify patient related factors that are associated with a higher amount of degeneration.

METHODS

Subjects and data collection

In this study, meniscal tissue in three different conditions was collected, from different subject groups: traumatically torn meniscal tissue (from now on referred to as TM), intact meniscal tissue (from now on referred to as IM), and osteoarthritic meniscal tissue (from now on referred to as DM). Traumatically torn meniscal tissue was collected during APM. Inclusion criteria were as follows: age under 45 year, history of a traumatic event in the last 6 months followed by clinical knee complaints, an MRI-proven meniscal tear without signs of knee OA, and an indication for APM. As a control group, intact meniscal tissue was collected during acute trans-femoral amputation or post-mortem dissection. Inclusion criteria were: age between 18 and 70 year, no history of knee injury, no radiological or clinical signs of knee OA, and no signs of knee OA at macroscopic inspection of the meniscus. Menisci from patients with vascular- or inflammatory diseases involving the knee or with systemic diseases were excluded. Inclusion criteria for degenerative osteoarthritic meniscal tissue were: age above 18 years, radiographically confirmed knee OA, and indication for total knee replacement surgery. Osteoarthritic meniscal tissue was used as reference standard, representing degenerative meniscal tissue.

Data was collected on the patient characteristics age, sex and body mass index (BMI). In the TM group, additional information was collected on time interval between trauma and surgery, and on associated anterior cruciate ligament (ACL) ruptures. This study was approved by the Medical Ethics Committee of the Erasmus MC University Medical Center (MEC-2004-322 and MEC-2015-180).

Meniscal tissue processing

Directly after harvesting, meniscal tissue was stored in formalin fixative (formaldehyde 4%). Tissue was processed within 1-3 days after surgery in a standardized way, according to the method of Pauli et al. [23] (Figure 1). Meniscal tissue was cut into two different planes in 5 mm-samples. The sagittal (i.e., vertical) cut, oriented perpendicular to the circumferential collagen bundles, provided an overview of the meniscal surface and matrix composition. The horizontal cut, at a 30° angle relative to the tibial plateau, revealed the longitudinal organization of collagen bundles and matrix morphology (Figure 1). Samples were further processed by dehydration and infiltration with paraffin, followed by cutting them into 6 µm-sections using a microtome (Leica Microsystems). Subsequently, the sections were stained with hematoxylin and eosin (H&E, Sigma) to assess surface integrity and cellularity. Additionally, Safranin O-Fast Green and Picrosirius Red (Sigma) staining was applied to analyze proteoglycan content of the meniscus and collagen fiber organization, respectively.

Figure 1. Harvesting meniscal tissue. A) Meniscal tissue after resection of a medial bucket handle tear in 24-year-old male. B) vertical cut from the posterior horn. C) horizontal cut from the posterior horn.

Histological analysis

All meniscal sections were scored using the validated histological scoring system for meniscal degeneration by Pauli et al. [23] (Figure 2). The Pauli score contains the following subdomains: surface integrity (tibial surface, femoral surface, and inner rim), cellularity, collagen organization, and matrix staining intensity. A score ranging from 0 to 3 (depending on the degree of degeneration) was assigned in each subdomain, resulting in a total histologic score ranging from 0 to 18. Scoring of the samples was performed independently by two researchers (MW & SE), blinded to condition, region of the meniscal tissue, and patient data. Three weeks after initial evaluation, one researcher (MW) scored the sections again. The latter scores were exclusively used to calculate intra-observer reliability.

Statistical analysis

Baseline characteristics for each subject group (i.e., TM, IM, and DM) were collected and tested for normality using Shapiro-Wilk tests. Depending on data distribution, differences in continuous data between groups were assessed using one-way ANOVA or Kruskal-Wallis tests, followed by post hoc Wilcoxon Rank Sum analysis with Bonferroni correction. Categorical data were analyzed using a Fisher's exact test with Bonferroni correction for pairwise comparisons. Inter- and intra-observer reliability of histological scoring was evaluated using intraclass correlation coefficients (ICC). A two-way mixed model based on absolute agreement for single measures was used. Reliability was regarded as excellent if ICC > 0.75. [24]

To investigate and correct for potential confounding variables within the subject groups, a multiple linear regression model was designed. Based on existing literature on potential factors associated with meniscal degeneration or osteoarthritis, the variables age, sex, and BMI [23,25,26] were included in a forced-entry analysis. Univariate linear regression analysis was performed within the TM group on the variables "time interval between trauma and surgery", and "associated anterior cruciate ligament rupture" to assess their association with histological scores. In case an association was found for those variables, they were included to the multivariate model.

All statistical analysis included two tailed tests. A P value of < 0.05 was considered to indicate statistical significance. SPSS statistics package version 21.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for all analysis.

1. Surface integrity		
	Femoral surface	**Score**
	• Smooth	0
	• Slight fibrillation	1
	• Moderate fibrillation	2
	• Severe fibrillation	3
	Tibial surface	
	• Smooth	0
	• Slight fibrillation	1
	• Moderate fibrillation	2
	• Severe fibrillation	3
	Inner rim	
	• Smooth	0
	• Slight fibrillation	1
	• Moderate fibrillation	2
	• Severe fibrillation	3
2. Cellularity		
	• Normal	0
	• Hypercellularity	1
	• Diffuse hypocellularity	2
	• Acellular	3
3. Collagen organization/alignment and fiber organization		
	• Collagen fibers organized	0
	• Collagen fibers organized and foci of mucinous degeneration	1
	• Collagen fibers unorganized and foci of mucinous degeneration	2
	• Collagen fibers unorganized and fibrocartilaginous separation	3
4. Matrix staining (Safranin O-Fast Green)		
	• None	0
	• Slight	1
	• Moderate	2
	• Strong	3

Note: the range of possible total scores is 0 – 18. The total score can be converted to a grade as follows: grade 1 = 0-4 (normal), grade 2 = 5-9 (mild degeneration), grade 3 = 10-14 (moderate degeneration), grade 4 = 15-18 (severe degeneration). In the present study, the Pauli score was used as continuous measure; no conversion to grades was performed.

Figure 2. Histopathological scoring system for meniscal degeneration by Pauli et al.

RESULTS

Patient characteristics

In total, 65 meniscal tissue samples were analysed: 43 traumatically torn samples, eight intact menisci, and 14 degenerative menisci. Due to limited sample sizes in each subject group, most data were non-parametric and was reported as median with interquartile range. Baseline characteristics, stratified per subject group, are summarized in Table 1. The median age was 29 years in the TM group, 58 years in the IM group, and 66 years in the DM group. Statistically significant differences in age were encountered between the TM and IM group ($P = 0.001$), and the TM and DM group ($P < 0.001$). Age was not different between the IM and DM group. The median BMI in the TM group (23.6 kg/m^2) was statistically significantly lower than the DM group (28.4 kg/m^2, $P = 0.043$. BMI in the IM group (29.7 kg/m^2) was not

different from the TM or DM group. A statistically significant higher percentage of males was present in the TM group compared to the DM group (79% versus 29%, P = 0.003). No difference in sex distribution was observed in both subject groups compared to the IM group (38%). The median time interval between trauma and surgery in the TM group was 13 weeks. 40% of the latter patients had a history of ACL rupture in their index knee.

Table 1. Characteristics of patients in traumatic, intact and degenerative group.

Characteristics	Traumatic meniscal tear (n = 43)	Intact meniscus (n = 8)	Osteoarthritic meniscus (n = 14)
Age at time of surgery in years†	29 (22 - 40)[1,2]	58 (54 - 64)[1]	66 (63 - 70)[2]
Body mass index (kg/m²)†	24 (22 - 26)[2]	30 (22 - 36)	28 (24 - 32)[2]
Sex‡			
Male	34 (79%)[2]	3 (38%)	4 (29%)[2]
Meniscal region examined‡			
Medial posterior horn	28 (65%)	8 (100%)	12 (86%)
Medial midbody	6 (14%)		
Lateral posterior horn	7 (16%)		1 (7%)
Lateral midbody	1 (2%)		
Lateral anterior horn	1 (2%)		
Unknown			1 (7%)
Time between injury and surgery (weeks)†	13 (6 - 30)		
History of ACL-rupture‡*:*	17 (40%)		
Bucket handle tear‡*:*	23 (54%)		

† Continuous data are presented as median (interquartile range)
‡ Categorical data are described as frequency (percentage)
1 Statistically significant difference between traumatic and intact group p <0.05
2. Statistically significant difference between traumatic and osteoarthritic group p<0.05
Abbreviations: ACL = anterior cruciate ligament

Histological analysis

Representative histological images, illustrating the range of histological scores, are presented in Figure 3. The overall scores in each subdomain are reported in Figure 4. The mean histological score in the TM group was 4.4 ± 2.2 (range 0-9), in the IM group 3.2 ± 1.6 (range 1-6), and in the DM group 7.1 ± 2.9 (range 2-12) (Figure 4).

Inter-observer reliability for histological scoring based on absolute agreement was excellent (ICC 0.95, 95% Confidence Interval (CI) 0.86-0.99). Similar findings were observed regarding intra-observer reliability (ICC 0.96, 95% CI 0.90-0.98).

Multivariate analysis on histological scores

To identify and adjust for potential confounders between subject groups, a multivariate linear regression analysis was performed (Table 2). After adjustment for age, sex, and BMI, menisci in the TM group showed a statistically significant higher histological score compared to the IM group (2.7 point higher ± 1.3, P = 0.035). Furthermore, the adjusted histological score

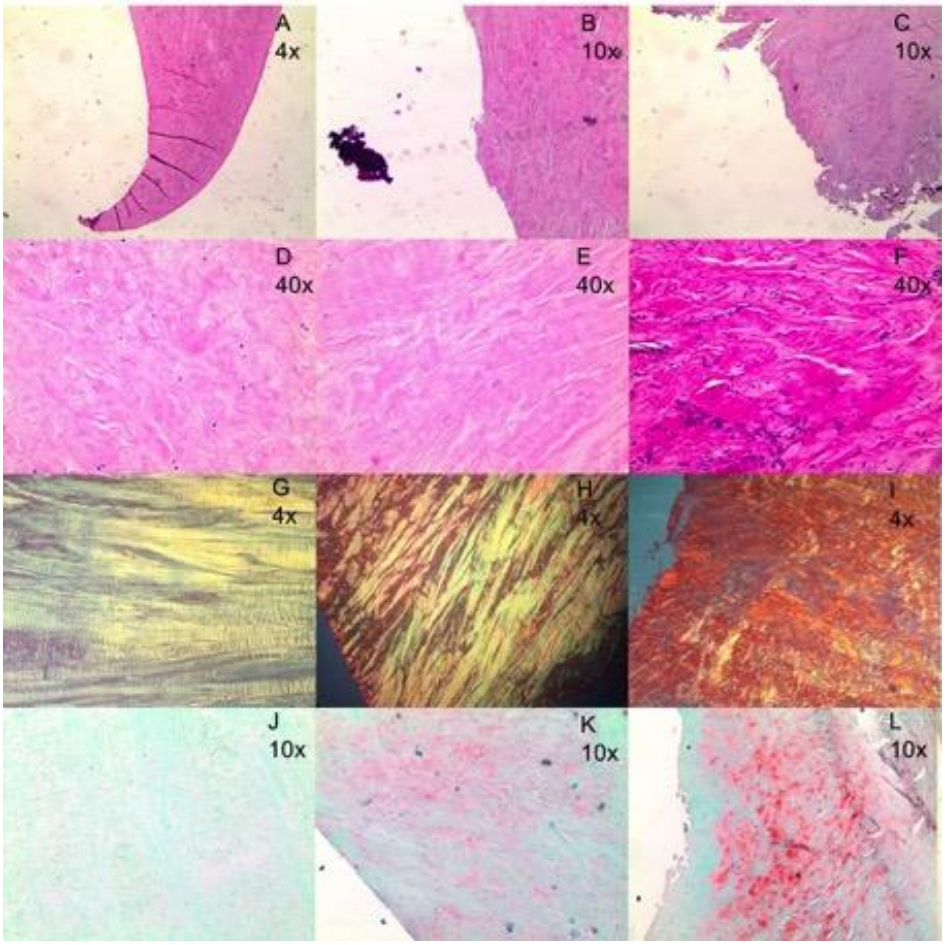

Figure 3. Representative examples of histological evaluation. A-C) Histological score 0, 1 and 2 (left to right) on subdomain *surface integrity*, Hematoxylin and Eosin staining. D-F) Histological score 0, 1 and 2 (left to right) on subdomain *cellularity*, Hematoxylin and Eosin staining. G-I) Histological score 0, 1 and 2 (left to right) on subdomain *collagen organization*, Safranin-O-Green staining. J-M) Histological score 0, 1 and 2 (left to right) on subdomain *matrix staining intensity,* Safranin-O-Green staining.

for the DM group was statistically significantly higher than those of the IM group (4.0 point higher ± 1.2, P = 0.001). The histological score of the TM group did not differ from the DM group, after adjustment. BMI appeared to be independently associated with histological score. An increase in BMI by one unit resulted in an increase of 0.16 ± 0.07 in histological score (P = 0.04) (Figure 5). The histological score and the variables age and sex were not associated.

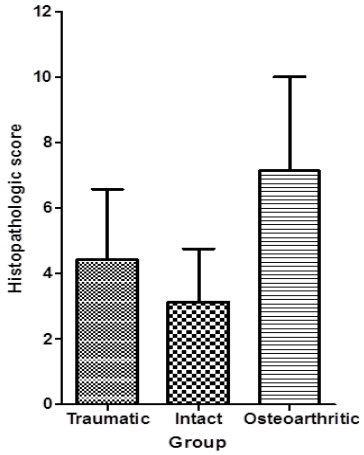

Figure 4. Histologic scores in traumatic meniscal tissue group, intact meniscal tissue group, and osteoarthritic meniscal tissue group. Data is presented as mean, vertical bar represents standard deviation.

Effect of "time interval between trauma and surgery" and "ACL rupture" on degree of degeneration in TM group

Univariate regression analysis revealed an increase of 0.21 ± 0.09 point in histological score for each unit in BMI increase (P = 0.03). No association was found between the histological score and the independent variables age at time of surgery, sex, meniscal region, time interval between trauma and surgery, and ACL rupture (Table 3).

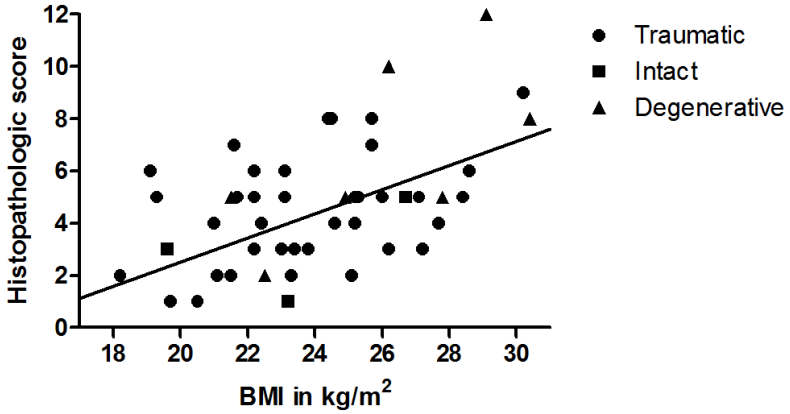

Figure 5. Correlation between BMI and histological degree of degeneration. Scatter plot showing correlation between BMI and histological score. Each symbol represents a unique sample. Abbreviations: BMI = body mass index.

Table 2. Multivariate analysis of risk factors on histologic score.

Characteristics	Regression coefficient	SE of regression coefficient	p-value
Age at time of surgery	0.02	0.03	0.497
Sex (female)	-0.88	0.66	0.190
Body mass index	0.16	0.07	0.040
Trauma group	2.73	1.26	0.035
Osteoarthritic group	3.97	1.16	0.001

Note: The intact meniscal tissue group is the reference group in the analysis.
Abbreviations: SE = standard error

Table 3. Univariate analysis of risk factors on histologic score in traumatically torn meniscal tissue group.

Characteristics	Regression coefficient	SE of regression coefficient	p-value
Age at time of surgery	-0.01	0.03	0.84
Sex (female)	-0.53	0.82	0.52
Body mass index	0.21	0.09	0.03
Timespan trauma to surgery	0.00	0.01	0.98
History of ACL rupture	1.06	0.64	0.10

Abbreviations: SE = standard error, ACL = anterior cruciate ligament

DISCUSSION

In this study, we assessed the degree of degeneration in traumatically torn-, intact- and osteoarthritic meniscal tissue, using a validated histological scoring system. Traumatically torn meniscal tissue showed a higher degree of degeneration than intact menisci. We identified BMI as an independent risk factor for meniscal degeneration. No clear association was observed between histological degree of degeneration and age, sex, or time interval between trauma and surgery.

To our knowledge, this is the first study assessing histological degeneration in different meniscal conditions. Most previous studies focused on one feature of degeneration. Mesiha and colleagues[26] reported that TM showed equal histological scores to DM. Their main outcome measure to assess degeneration was cellularity; low cellularity was observed in both TM and DM tissue. In a study by Meister et al. [14], Safranin-O matrix staining intensity (as a measure of the amount of glycosaminoglycans) was assessed and was found to be increased in patients with a traumatic meniscal tear [14]. In osteoarthritic menisci, the number of glycosaminoglycans is increased [27,28]. Therefore, the observed Safranin-O staining intensity in our study is regarded as a sign of degeneration of the meniscus. Collagen organization was disturbed in our traumatic meniscal tear samples. Park et al. [29] earlier concluded that torn meniscal tissue showed less organization of the collagen bundles and a lower amount of

collagen type I. Despite the fact that their research was done in a cohort of knee OA patients, torn meniscal tissue showed more disturbance of collagen alignment compared to patients without a tear. These findings may suggest that tissue quality plays an important role in the risk of a meniscal tear in the context of a traumatic event.

Much is unclear regarding the role of meniscal degeneration in traumatic meniscal tears. Currently, the most common view is that the majority of traumatic meniscal tears are the result of a tibiofemoral rotational force as the knee moves from flexion to extension or vice versa, while bearing weight [3]. Snoeker et al. showed that swimming was a risk factor for a meniscal tear too [25], thus suggesting that a large force transmission is not necessary in the occurrence of a "traumatic" meniscal tear. This highlights that classifying tears is not as straight forward as it seems. A more plausible view may be the earlier mentioned continuum theory: from a healthy to a degenerative meniscus. In this view, the chance to get a "traumatic meniscal tear" (partly) depends on the pre-existing degree of meniscal degeneration. That is, the more degeneration, the higher the risk of a torn meniscus in case of a traumatic event. The first clue for this theory was provided by the finding that older US Military servants showed a higher rate of meniscal injuries despite being exposed to the same activities and movements as their younger colleagues. Jones et al. concluded that the higher rate of injuries was related to degeneration of the meniscus as age increased [30]. Our findings challenge the classic view of "traumatic" versus "degenerative" meniscal tears and support the continuum theory in which degeneration of the meniscal tissue plays a major role in the risk of a meniscal tear organization [31].

In the present study, BMI was found to be independently correlate with the degree of meniscal degeneration. Previous clinical studies concluded that higher BMI is associated with a greater risk of a meniscal tear [7,25,32,33]. The effect of BMI on degeneration of the meniscus can be explained by its biomechanical role. An increase in BMI results in a greater force transmission by the meniscus [4]. Moreover, a higher BMI results in chronic inflammation of the knee joint. A chronic inflammatory state leads to an increase in metallo matrix protease production and degradation of collagen fibers [34,35]. This could be a partial explanation of the degenerative changes that occur in meniscal tissue. BMI might be used as a predictive factor of the degree of degeneration of the meniscus. Interestingly, we found no association between age and degree of degeneration of the meniscus, contradictory to previous evidence [23,26]. A possible explanation could be that in most previous studies the potential confounding effect of BMI regarding other factors and condition of the meniscus was not taken into account. It is well known that, when age increases, BMI increases as well [36-38]. In our study, after univariate testing of potential patient specific determinants, an association between age and histologic degeneration was observed. However, adjusted for BMI, this association lost significance (data not shown). Therefore, BMI might be a better explanation for a higher degree of degeneration instead of age.

Time interval between trauma and surgery showed no association with the degree of degeneration in the TM group. These findings are consistent with a previous study [26], which reported no differences in cell density and histological score with respect to time interval between trauma and surgery. Our findings suggest that degenerative changes did not change after the injury and might have been present before the injury occurred. However, critical interpretation of this finding is important given the cross-sectional study design without intra-subject longitudinal evaluation of the meniscal tissue composition. Moreover, literature shows that a meniscal tear has effects on other structures of the joint. This corresponds with the idea that a meniscal tear results in cartilage loss and thus accelerated development knee OA [39-42]. The loss of cartilage is greater in patients with a resected part of the meniscus, compared to patients without resection [43]. Englund et al. showed that knees with meniscal tears on MR imaging but without cartilage lesions were at higher risk of radiographic development of knee OA in later life than intact menisci. This implicates that visible meniscal damage occurs before visible cartilage changes [40,44]. These findings warrant careful decision making in the choice of treatment, and in case of APM timing of surgery.

The present study has some limitations that should be considered. First, we included only eight intact menisci (IM), due to the low incidence of acute trans-femoral amputations, especially in a younger population. Second, results on the subdomain "surface integrity" may be influenced by meniscal tears, affecting the meniscal surface. Nevertheless, a macroscopically intact portion of the meniscus was sectioned without the edge of the tear if possible.

In conclusion, we found a higher degree of meniscal degeneration in patients with a traumatic meniscal tear compared to intact menisci, and no association between time interval between trauma and surgery and histological score. A better understanding of the degeneration process is likely to help orthopedic surgeons decide on choice of treatment. This knowledge may also lead to new perspectives to prevent OA of the knee in patients with a torn meniscus after a traumatic event. Future studies should explore the possibilities of longitudinal *in vivo* evaluation of degeneration using for instance quantiitaivie MRI techniques.

Acknowledgements

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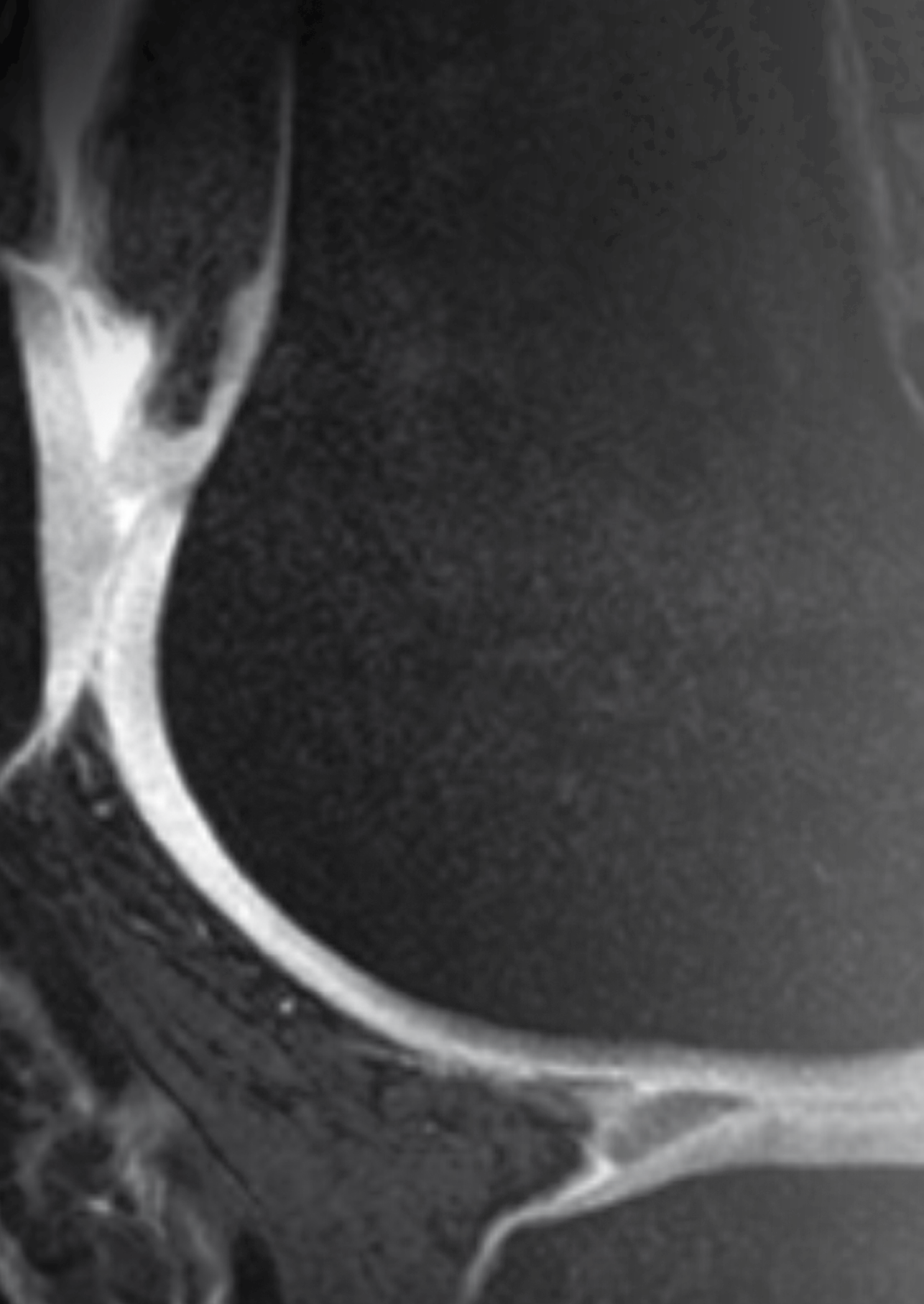

Chapter 7

Rationale and design of the STARR trial: should a traumatic meniscal tear be resected? - a randomized controlled trial

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Submitted for publication

ABSTRACT

Objective: Arthroscopic partial meniscectomy is the most performed orthopedic intervention. However, evidence is lacking regarding the efficacy of an arthroscopic intervention for traumatic meniscal tears. The primary objective of the presented study is to evaluate the (cost-) effectiveness of arthroscopic partial meniscectomy compared to a non-operative treatment strategy. The hypothesis is that an arthroscopic partial meniscectomy is a (cost-) effective intervention to treat patients with clinical complaints of the knee with a traumatic meniscal tear.

Methods: The STARR trial is an open-labelled randomized controlled trial. Patients aged 18-45 years with an MRI-verified meniscal tear and a recent history of trauma after which current knee symptoms developed, are eligible. Patients will be randomized to arthroscopic partial meniscectomy (control group) or a standardized exercise program under supervision of a physical therapist and pain medication if required (intervention group). The primary outcome measure is the change in clinical outcome measured with the International Knee Documentation Committee (IKDC) questionnaire over a two-year period. Secondary outcomes are the cost-effectiveness over the two-year period and early cartilage degeneration, measured by quantitative magnetic resonance imaging (T_2 mapping).

Discussion: The STARR trial will provide evidence concerning the (cost)-effectiveness of a partial arthroscopic meniscectomy compared to non-operative treatment for patients with clinical complaints of the knee with a traumatic meniscal tear. This study addressess an important evidence gap and the results will have great impact on clinical decision making in patients with a traumatic meniscal tear.

INTRODUCTION

Meniscal tears are among the most common knee injuries and are frequently found in younger and active persons [1]. The incidence of persons with meniscal tears presenting to an orthopedic trauma department is 23.8/100.000 per year [2]. Meniscal tears are traditionally classified into traumatic and degenerative tears. Patients with traumatic meniscal tears have a history of an acute onset (often during sport activities). Patients with degenerative meniscal tears tend to have a more gradually development of complaints.

Health care efficiency problem

Patients with complaints of a meniscal tear are limited in sport and daily activities, which influences the quality of life. So far, the natural course of these complaints is unknown. Eventually, the majority of the patients with a meniscal tear will develop osteoarthritis (OA) at relatively early age [3,4]. When a patient present to a physician with a symptomatic meniscal tear, decisions need to be made regarding the most optimal treatment. Treatments options for a meniscal tear are non-operative (i.e., exercise therapy, pain medication, relative rest) or operative (i.e., arthroscopic partial meniscectomy or meniscal repair). The treatment choice for patients with signs and symptoms of a meniscal tear should be based on benefits and disadvantages of potential interventions. First, the gain on symptom level should be considered. On society level, it is also worthwhile to take into account the medical and productivity costs of the chosen treatment. Furthermore, a meniscal tear is strongly related to the onset of osteoarthritis, therefore the potential influence of the chosen treatment on osteoarthritic changes should also be considered. Finally, in case of an operative intervention, the risk of potential peri-operative complications should be considered. Thus, the optimal treatment of the individual patient should be based on a weighted decision on the abovementioned effect levels. A recent systematic review based on several high-quality RCTs reported that an arthroscopic partial meniscectomy is not beneficial compared to exercise therapy or even placebo surgery for patients with a degenerative meniscal tear [5]. However, for patients with a traumatic meniscal tear there is a paucity of evidence whether an arthroscopic partial meniscectomy is the most optimal intervention.

Anticipated cost-effectiveness

In general, it can be said that young and active patients in the prime of their career will have considerable economic burden in time off work because of their meniscal tear. The potential clinical benefit of an effective arthroscopic procedure has to be weighed against the costs of a surgical procedure, rehabilitation costs, and costs due to potential surgical complications. An arthroscopic partial meniscectomy is financially fully covered by the health insurance in The Netherlands. Usual care in The Netherlands comprises that orthopedic surgeons perform an arthroscopic partial meniscectomy soon after the injury, and not later during the follow-

up after unsuccessful non-operative treatment. Additionally, nowadays an arthroscopic intervention has become more readily available because of an increasing number of private clinics.

Standard care

An arthroscopic partial meniscectomy remains the most frequently performed procedure by orthopaedic surgeons in The Netherlands, approximately 40.000 procedures yearly [6].

Trial objectives

In spite of the high frequency of performed arthroscopic partial meniscectomies, the (cost-) effectiveness of this procedure has been increasingly questioned. Especially, in case of a traumatic meniscal tear without a "fixed locked knee", the Dutch and other guidelines are not conclusive whether an arthroscopic intervention is the most optimal treatment. The aim of the present study proposal is to evaluate the (cost-) effectiveness of an arthroscopic partial meniscectomy in patients with a traumatic meniscal tear. An arthroscopic partial meniscectomy will be compared to non-operative treatment (i.e., exercise therapy and pain medication). Our hypothesis is that an arthroscopic partial meniscectomy is a (cost-) effective intervention to treat patients with clinical complaints of the knee because of a traumatic meniscal tear (superiority study).

Primary objectives:

1. To assess whether there is a clinically relevant effect of an arthroscopic partial meniscectomy compared to a non-operative treatment over a 2-year period in patients with a traumatic meniscal tear.
2. To assess whether an arthroscopic partial meniscectomy is a cost-effective intervention over a 2-year period in patients with a traumatic meniscal tear.

Secondary objectives:

1. To identify potential predictors for a clinically relevant better outcome of an arthroscopic partial meniscectomy over a 2-year period.
2. To assess whether there are differences in early cartilage degeneration on quantitative MRI over a 2-year period between an arthroscopic partial meniscectomy and non-operative treatment.

METHODS

Study design

The design of the present proposal is an open-labelled randomized controlled trial. Patients will be randomized into a group receiving arthroscopic partial meniscectomy (a); or in a group receiving non-operative treatment (b). Approval was obtained by the Erasmus MC Medical Ethics Committee (registration code NL46822.078.13). The study has been registered in the Dutch Trial Registry (registration number NTR4511.

Setting

The study will be conducted at the department of orthopedic surgery of Erasmus MC University Medical Center (Rotterdam), Máxima MC (Eindhoven/Veldhoven), Haaglanden MC (The Hague), Elisabeth Hospital (Tilburg), *St.* Antonius Hospital (Utrecht), Onze Lieve Vrouwe Gasthuis (Amsterdam), Catharina Hospital (Eindhoven) and Noordwest Hospital group (Alkmaar).

Study population

Inclusion criteria

In order to be eligible to participate in this study, a patient must meet the following criteria: age between 18 and 45 years; a history of a knee trauma (in the past six months) after which current knee complaints were initiated, and the presence of a meniscal tear (grade 3) on MRI.

Exclusion criteria

A potential subject who meets any of the following criteria are excluded from participation in the STARR trial: a fixed locked knee (i.e., when the patient is unable to extend or bend the index leg); a reparable meniscal tear (based on MRI, according to the patient's attending physician); rupture of the anterior or posterior cruciate ligament (in medical history or concurrent with meniscal tear); radiographic knee OA (based on radiograph and/or MRI); disabling co-morbidity; and insufficient command of Dutch or English language.

Recruitment

Patients, who visit the outpatient clinic of one of the participating hospitals and meet the inclusion criteria, are informed about the study by their orthopedic surgeon. The potential eligible patients receive written information and are invited to participate. If they are interested, the researcher contacts them and screen on in- and exclusion criteria. When the patient still conforms to the eligibility criteria and gives written informed consent, baseline measurements are carried out. Thereafter patients is randomized into one of the two treatment groups.

Randomization

Allocation to type of intervention takes place by receiving the consecutive randomization number from the coordinating investigator. A computer-generated randomization list is used (block randomization, with variable size of the blocks; stratified for orthopedic surgeon). After this the allocation of the type of intervention is open to the orthopaedic surgeon, and to the patient. Data analysis are obtained and analysed by the researcher who is blinded for group allocation and patient characteristics. After complete data analysis, unblinding will take place.

Interventions

Control arm: arthroscopic partial meniscectomy

Arthroscopic partial meniscectomy is performed within 6 weeks after randomization with the patient under general or spinal anesthesia and with the use of a tourniquet. During arthroscopy, the orthopedic surgeon evaluates all knee compartments on articular lesions according to the Outerbridge classification. Location and type of meniscal tears are registered, thereafter excision of the meniscal tear is performed. If during the arthroscopic procedure the orthopedic surgeon decides that suturing of the tear is indicated, this is allowed. According to Dutch guidelines of physical therapists and orthopedic surgeons, physical therapy is indicated solely in case of (expected) delayed recovery following meniscectomy and is performed accordingly.

Intervention arm: non-operative treatment strategy

A standard exercise program has been developed in collaboration with participating physical therapists and sport physicians, and patients are treated accordingly. The goal of the exercise program is to reduce pain, restore full range of motion and to restore knee function. It consists of exercises for improving muscle strength and endurance, muscle flexibility as well as balance and proprioception. The exercise therapy protocol takes about 12 weeks. There is no restriction regarding physical therapist in the STARR trial; patients are free to choose their therapist. The costs of exercise therapy are covered for patients who participate in the STARR trial; financial arrangements in this context are established with health insurance companies. The intensity of exercise therapy (i.e., frequency of therapy sessions and exercises per week) is determined by the attending physical therapist and the patient. At baseline, an information brochure comprising home exercises is provided to the patient by the researcher. A routine pain medication protocol is used [7].

Outcome measurement

Outcome measures used at the different time points can be found in Table 1.

Table 1. Summary of study timing and activities*

	STUDY PERIOD			
	Enrolment	**Allocation**	**Post-allocation**	**Close-out**
ENROLMENT	Baseline	Randomization	3, 6, 9, 12-months FU	24-months FU
Eligibility screening	X			
Informed consent	X			
Allocation		X		
INTERVENTIONS				
Intervention group: arthroscopic partial meniscectomy			X	
Control group: non-surgical treatment			X	
ASSESSMENTS				
Demographics: age, sex, side, BMI, education level, comorbidity	X			
IKDC questionnaire	X		X	X
KOOS questionnaire	X		X	X
WOMET questionnaire	X		X	X
Lysholm & Tegner questionnaire	X		X	X
NRS pain questionnaire	X		X	X
Satisfaction questionnaire				X
EQ-5D questionnaire	X		X	X
iMCQ and iPCQ questionnaire	X		X	X
MRI knee including T_2 mapping	X			X
Adverse events			X	X

* According to standard protocol items: recommendation for interventional trials (SPIRIT)
BMI = Body Mass Index, IKDC = International Knee Documentation Committee, KOOS = Knee injury and Osteoarthritis Outcome Score, WOMET = Western Ontario Meniscal Evaluation Tool, NRS pain = Numerical Rating Scale for pain, iMCQ = iMTA Medical Cost Questionnaire, iPCQ = iMTA Productivity Cost Questionnaire, FU = follow up
Standard protocol items: recommendation for interventional trials (SPIRIT)

Patient characteristics

At baseline, patient characteristics are obtained: age, sex, side affected (i.e., left or right), height, weight, education level, (musculoskeletal) comorbidity, duration of complaints, and previous surgery.

Primary outcome measure

The primary endpoint of the STARR trial is a clinically relevant difference in change in International Knee Documentation Committee (IKDC) questionnaire over a two-year period.

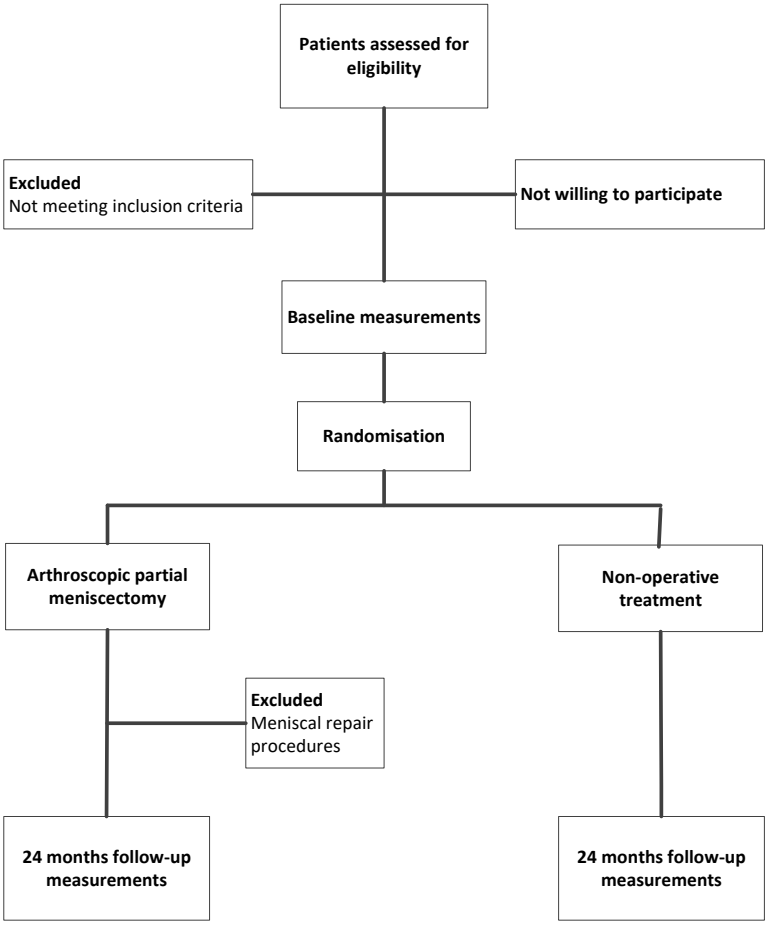

Figure 1. Flow diagram of the STARR trial, according to Consolidated Standards of Reporting Trials (CONSORT).

Main secondary outcome: cost utility

During the two-year follow-up, information regarding medical consumption (such as contact with general practitioner (GP), physical therapist, medical specialist, diagnostic imaging, arthroscopy and other knee procedures, hospital stay, medication, appliances, home modifications and home care), productivity loss due to the meniscal tear, and the amount of informal care provided are collected. Data on the amount of medical consumption within the hospital is collected by the researcher. We register all medical procedures, diagnostic imaging, and length of stay. Non-hospital medical consumption and patient travel costs is collected using the iMCQ patient questionnaire (iMTA Medical Cost Questionnaire) [8] at all timepoints as described above. The questions refer to GP contact, contact with physicians from other hospitals, physical therapists, manual therapists, other paramedics, home care, medication (especially pain medication), hours of informal care, etc. Productivity costs are measured

using the iPCQ (iMTA Productivity Cost Questionnaire) [9] at all measurement moments. The cost per unit of medical consumption, patient time, informal care and per hour of work lost are estimated, using updated information from the Dutch Manual for economic evaluation of health care [10].

The most important patient outcome for the cost utility is quality of life, which will be measured by means of the EQ-5D instrument. The EQ-5D comprises five dimensions: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. Utility values of the general Dutch public for these health states will be applied in this study [11]. Two cost utility ratios are calculated: incremental medical costs per QALY gained of arthroscopic partial meniscectomy versus non-operative treatment; incremental societal costs per QALY gained of arthroscopic partial meniscectomy versus non operative treatment. The societal costs include: medical costs, productivity costs and patient costs.

Other outcome measures

Secondary clinical outcomes in the STARR trial are differences in scores of the Knee injury and Osteoarthritis Outcome Score (KOOS), Western Ontario Meniscal Evaluation Tool (WOMET), work- and sports load (Lysholm, Tegner), Number rating Scale for knee pain (NRS), and patient satisfaction. Measurements take place after 3, 6, 9, 12 and 24 months of follow-up. A standardized MRI examination of the knee is obtained at baseline and at two-year follow-up. Semi-quantitative MRI assessment of the whole knee, using the MRI OA Knee Score (MOAKS) as advised by the Osteoarthritis Research Society International (OARSI), is used as outcome measure [12]. To quantify early stages of cartilage degeneration, changes in composition and matrix integrity of cartilage are evaluated using quantitative MRI (T_2 mapping). Other secondary outcomes are use of pain medication and presence of adverse events.

Sample size and power calculations

Sample size calculation for the STARR trial was performed using the studies of Barber and Rodkey [13,14]. Barber et al. reported preoperative data of patients with eligibility criteria similar to the STARR trial with a mean Lysholm score of 47.3 (SD of 29.9). Rodkey reported mean change in Lysholm score after two-year follow-up of 28 (SD not provided). A surgical intervention should have a clinically relevant additional effect compared to a non-operative approach. Clinically relevant difference is defined as a difference between both groups of minimally 15 points (effect size 0.5). For a power of 80% with an alpha of 0.05, the required sample size is 63 patients per intervention group; thus, a total of 126 patients. To accommodate 15% potential dropout rate over the 2-year follow-up and to compensate for per-operative conversions from meniscectomy to meniscal repair (an estimated 5% of STARR participants in the arthroscopy group), our initial aim was to include 152 patients. However, based on lower actual dropout rate and the standard deviation of included study population, we recalculated the required sample size, in agreement with the trial sponsor. With 100

patients, a clinically relevant additional effect of an effect size of minimally 0.5 of a surgical intervention can be detected, with the same assumptions of a power of 80% and an alpha of 0.05 (two-sided testing).

Feasibility of recruitment

Phase 1 [15]: Each of participating hospitals perform approximately 100 (range 70-180 per Hospital) arthroscopic partial meniscectomies yearly. We checked records of patients with a meniscal tear who visited an orthopedic surgeon in Erasmus MC University Medical Center or Haaglanden MC during the past two years on eligibility criteria. Yearly around 60-110 patients fulfilled these criteria. Hence, we expected that recruiting 152 patients should be feasible in 15 months.

Phase 2: Two orthopedic surgeons from participating hospitals are project members of the STARR trial and were extensively involved with the development of this proposal. Our institution has built up extensive experience regarding including patients for clinical studies. The hospitals participating in the STARR trial have participated in previous studies of our group. Each hospital has concentrated the appointments of young patients with acute knee complaints at their outpatient clinic. Consequently, it will be feasible for the researcher to be present at each location when potential eligible patients will be seen at the outpatient clinic of participating hospitals. Prior to the start of the study, clear arrangements will be made with participating orthopedic surgeons regarding co-authorship in future scientific publications. The researcher will perform all measurements and will be responsible for all logistics.

Phase 3: Because of the absence of an adequate patients' association regarding meniscal tears, we composed a FOCUS group of patients with a recent knee trauma. The information form for patients has been evaluated by patients of this group.

Data management

All patient data are handled confidentially and anonymized in compliance with the Dutch Personal Data Protection Act ("Wet Bescherming Persoonsgegevens"). Questionnaires are collected digitally, and the patient study data are stored in a coded way using secured data management software (Gemstracker version 1.6.3, Erasmus MC, Rotterdam, the Netherlands). Each patient gets an anonymized study number that is used for all documentation, study reports and publications. The key to this study number is handled by an independent researcher. All data will be stored during the study period, after the study is finished the data will be stored for 15 years in the Erasmus MC University Medical Center secured research archive.

Statistical analysis

Analysis of STARR trial outcomes will primarily be performed by "intention to treat". That is, all participants randomized in the STARR trial will be included in the analysis according to

their treatment allocation, even if they did not receive the intervention they were allocated to receive. A secondary analysis will be performed, limited to the participants that were compliant to the treatment protocol of the groups to which they were randomized (i.e., per protocol analysis). Distribution analysis of all variables will be tested using Shapiro-Wilk tests. For normally distributed variables, parametric tests will be used. For non-normally distributed variables, nonparametric test will be used.

Primary study parameters

The difference between intervention groups in mean change in IKDC score after two years will be used as primary outcome. Primary analyses will be performed using repeated measurements for linear regression analysis. Fixed effects will be the variable "time", and the covariates we adjust for. For patients who are lost to follow-up, we will include all observed data in the analysis. Adjustment will be done for those baseline variables that change the effect estimate with more than 10%. If necessary, adjustments for unbalanced covariates will take place. The assumptions of constant variance and linear relationships will be assessed using scatterplots. Should any of these assumptions seriously fail then variable transformations of the dependent or independent variable(s) (where applicable) will be used. The choice of which transformation (e.g. square root, logarithm) will be used based on the specific distribution of the residuals.

Secondary study parameters

Predictors for a clinically relevant better efficacy over a two-year period of an arthroscopic partial meniscectomy will be identified by using logistic regression analyses (clinically relevant increased effect over a period of 2 years as dependent variable). Variables of which a priori is known that they are associated with patient satisfaction, based on previous studies or based on a strong clinical rationale, will be considered covariates in the primary analysis. Whether an arthroscopic partial meniscectomy can decrease the risk of early degenerative changes compared to a non-operative treatment, will be analyzed by using logistic regression analyses. The presence of early degenerative changes will be assessed by quantitative MRI (T_2 mapping) and semi-quantitative MRI OA Knee Score (MOAKS).

Cost-effectiveness analyses

By means of non-parametric bootstrapping (i.e., drawing 2500 observations at random from the available patient sample), the degree of uncertainty for costs and health effects and the cost utility ratio will be depicted on the so-called cost-effectiveness plane. In addition, an acceptability curve will be drawn, which indicates the probability that the health care program has lower incremental costs per QALY gained than various thresholds for the maximum willingness to pay for an extra QALY.

Budget impact analysis (BIA)

In the budget impact analysis, we will compare the budget impact for the government, health insurers and patients for the following scenarios: arthroscopic partial meniscectomy; a non-operative strategy (with an immediate reduction of maximally 40% of 40,000 surgical interventions) and a gradual decrease in surgical interventions.

Cost analysis

When the number of meniscectomies would reduce, patients will be more often treated with physiotherapy (at least 10 sessions per patient, which might (or not) be reimbursed by supplementary health insurance). We wil closely examine the reduction in surgery and the probability of substitution care. The annual budget impact for each scenario mentioned above will be calculated from the perspective of the government, both using the societal costs (direct and indirect costs, with prices from the manual cost calculation, and using the prices of the Dutch Healthcare Authority. For the perspective of the health insurer and the patients we will use the Dutch Healthcare Authority tariffs and co-payments when applicable.

DISCUSSION

The STARR trial is the first trial to analyses the (cost-) effectiveness of partial arthroscopic meniscectomy compared to non-operative treatment strategy, in patients aged 45 year or younger with a traumatic meniscal tear.

An arthroscopic partial meniscectomy is the most frequently performed procedure by orthopedic surgeons in The Netherlands; over 40.000 procedures yearly [6] . Because of an increasing number of private clinics, this procedure has become more readily available. Due to the fact that only around 5% of the meniscal tears are suitable for meniscal repair [16], a partial meniscectomy is still the most performed surgical procedure for a meniscal tear. The main evidence of the effectiveness of a meniscectomy is based on studies in patients with degenerative meniscal tears with already signs of OA [17]. For these so called degenerative meniscal tears the evidence is clear; the guidelines recommend therefore that a meniscectomy is not indicated as an initial treatment for degenerative tears. However, for young and active patients with a meniscal tear due to a trauma, the evidence is limited, and the effectiveness of this procedure is increasingly questioned. The current evidence of the effectiveness of a meniscectomy in young and active patients is based on retrospective studies [17] and one small RCT which compared the effectiveness of arthroscopic partial meniscectomy with a non-surgical therapy in patients with clinical symptoms of a traumatic meniscal tear [18]. These studies suggest that a partial meniscectomy is an effective intervention for those patients on the short term. However, after surgical removal of the damaged parts of meniscal tissue, knees are at high risk for the long-term development of OA [19,20] . On the other hand, also

without surgical intervention, meniscal damage is a potent risk factor for the development of OA [3,21]. Thus, there is a clear need for well-designed studies investigating the effectiveness of an arthroscopic partial meniscectomy for young and active patients with a meniscal tear.

Strengths of the study include the solid methodological framework, in which patient will be randomly assigned to partial arthroscopic meniscectomy or non-surgical treatment. Secondly, the study has a pragmatic design in which both interventions are frequently used in daily clinical practice. This aids to the generalizability of the study results, limits the burden for the study population and increases the likelihood for patients to be willing to participate.

A challenge of the proposed study is that some patients and also orthopedic surgeons might have problems with committing to the randomization process. This is a more often seen in surgical trials, in which a surgical intervention will be compared to a non-surgical intervention.

Trial status

The study inclusion has started in August 2014.

Declaration

Ethics approval and consent to participate

The study has been reviewed and approved by the Medical Ethics Committee (registration code NL46822.078.13) of the Erasmus MC. All participants signed a written informed consent form prior to start of the testing procedures.

Consent for publication

No individual person's data will be published, therefore consent for publication is not applicable.

Competing interests

The authors declare that they have no competing interests.

Funding

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Trial sponsor

The Netherlands Organization for Health Research and Development (call efficiency studies)

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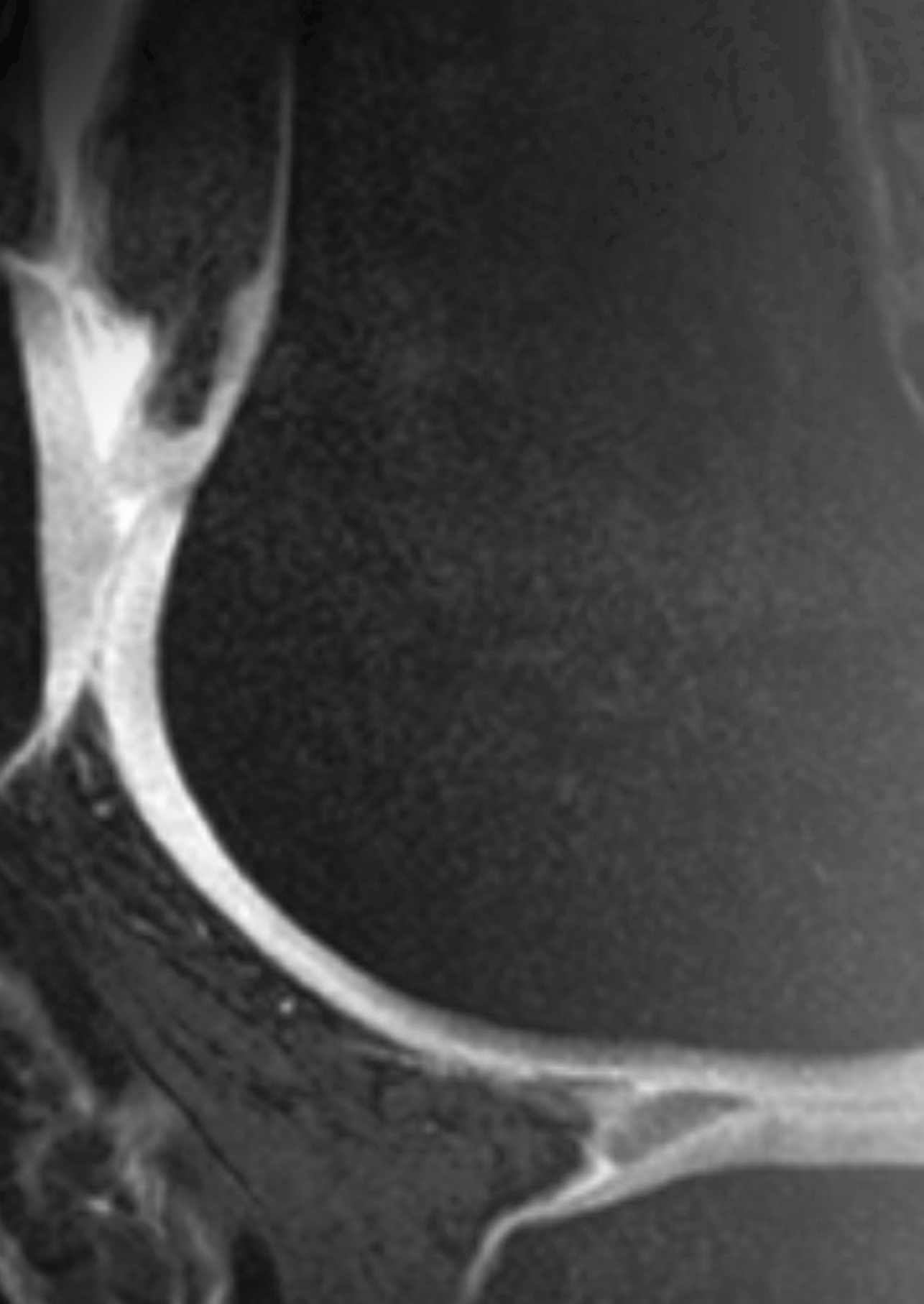

Chapter 8

Can we predict the clinical outcome of arthroscopic partial meniscectomy? - a systematic review

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ABSTRACT

Objective: In order to make a more evidence-based selection of patients who would benefit the most from arthroscopic partial meniscectomy (APM), knowledge of prognostic factors is essential. We conducted a systematic review of predictors for the clinical outcome following APM.

Methods:
Design: Systematic review
Data-sources:Medline, Embase, Cochrane Central Register, Web-of-science, SPORTDiscus, Pubmed Publisher, Google Scholar
Inclusion criteria: report an association between factor(s) and clinical outcome; validated questionnaire; follow-up >1 year
Exclusion criteria: <20 subjects; ACL-deficient patients; discoid menisci; meniscus repair, -transplantation or -implants; total- or open meniscectomy
Data-extraction and analysis: Two reviewers extracted the data, assessed the risk of bias and performed a bestevidence synthesis

Results: Finally, 32 studies met the inclusion criteria. Moderate evidence was found, that the presence of radiological knee-osteoarthritis at baseline and longer duration of symptoms (>1 year) are associated with worse clinical outcome following APM. In addition, resecting more than 50% of meniscal tissue and leaving a non-intact meniscal rim after meniscectomy are intra-articular predictive factors for worse clinical outcome. Moderate evidence was found that sex, onset (acute or chronic), tear type or pre-operative sport level are no predictors for clinical outcome. Conflicting evidence was found for the prognostic value of age, perioperative chondral damage, BMI and leg-alignment.

Conclusion: Long duration of symptoms (>1 year), radiological knee-osteoarthritis and resecting >50% of meniscus are associated with a worse clinical outcome following APM. These prognostic factors should be considered in clinical decision making for patients with meniscal tears.

INTRODUCTION

A meniscal tear is a very common injury, with an incidence of patients visiting an orthopedic trauma department of 24/100.000 per year [1]. The main symptoms are pain, swelling and dysfunction of the knee. A meniscal tear can be the result of a traumatic event or due to degeneration. Both non-operative and operative treatment options are available. Non-operative treatment mainly involves exercise therapy and pain medication, whereas operative treatment of meniscal tears involves either arthroscopic partial meniscectomy (APM) or, in some cases, repair of the torn meniscus if feasible. For many years, APM has been considered the gold standard for torn menisci, for both traumatic and degenerative tears [2,3]. Yearly, over 700.000 APMs are performed in the U.S. [4].

Although it is still one of the most common surgical procedures in many Western countries [5], several recently published high-quality RCTs challenge the indications of APM [4,6-9]. These trials, summarized in a recent systematic review [10], consistently show no benefit of APM compared to physical therapy or sham surgery in patients with degenerative meniscal tears. Furthermore, there is a growing concern that patients who have undergone APM are at increased risk of developing knee osteoarthritis (OA) [2,11].

Taking the results of the earlier mentioned RCTs and the concern about knee OA into account, a more evidence-based approach in patient selection for APM is needed. Instead of considering APM the standard of care, clinicians need to carefully select subgroup of patients with meniscal pathology who would likely benefit from APM. If one can predict the chance of success following APM based on patient characteristics, a more evidence-based patient selection can be made. In order to predict this chance of success, knowledge of prognostic factors is essential.

To the best of our knowledge, no systematic review of prognostic factors for the clinical outcome following APM has been conducted. We systematically reviewed all available literature, to determine the association between certain preoperative and operative variables and clinical outcome following APM. The purpose of this study was to identify prognostic factors for the clinical, patient-reported outcome of APM in patients with a meniscal tear.

METHODS

The reporting in this systematic review was conducted according to the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA) statement [12]. This study was registered in the International Prospective Register for Systematic Reviews (Prospero) of the National Institute for Health Research (NHS), no. 42016048592.

Search strategy

A health science librarian of our institution with extensive experience in the conduct of literature searching for systematic reviews assisted in designing and performing the search. We searched in Medline, Embase, Cochrane Central Register, Web of Science, SPORTDiscus, PubMed Publisher, and Google Scholar for relevant articles (date of search: September 16th, 2016). The following main keywords were used: knee, meniscus, meniscal tear, treatment, and meniscectomy (see Supplementary material 1 for complete search). The articles types included in the search were randomized controlled trials and prospective or retrospective cohort studies. There was no date of publication restriction in the search.

Study selection

The inclusion criteria for the present study were: 1) all subjects had to have a meniscal tear, confirmed by MRI (Magnetic Resonance Imaging)/arthroscopy/X-ray with contrast, treated with APM; 2) subjects had to be over 18 years of age; 3) the study had to describe a correlation/association between certain prognostic factor(s) and clinical outcome of APM; 4) a validated patient reported outcome measure had to be used; 5) there had to be a follow-up of at least 12 months; and 6) the article had to be written in English, German, Dutch, French, Spanish, or Swedish. We choose these languages because members of the project group were able to read these.

We excluded studies which; 1) had less than 20 subjects; 2) included patients with ACL-deficiency or with previous ACL-reconstruction; 3) included patients with discoid menisci; 4) included patients undergoing meniscal repair; 5) included meniscus transplantation or meniscus implants; 6) included patients undergoing total meniscectomy; 7) included patients undergoing open meniscectomy; and 8) included additional surgical interventions carried out at arthroscopy.

Two reviewers independently screened all titles and abstracts for eligibility. Disagreements were discussed and resolved by consensus. A third reviewer was asked in case of unsolved disagreement. Duplicate studies were manually removed. Furthermore, reference lists of all selected studies were searched to identify potential missed articles.

Risk of bias

To assess the potential risk of bias, two reviewers independently assessed each study using the Cochrane Collaboration's tool for assessing risk of bias of prognostic studies [13,14]. This scoring list involves eight questions; two questions concerning selection bias, three questions concerning information bias, and two questions concerning confounding. A low risk of bias was defined as 1) ''yes" to at least 70% of the questions (6 out of 8 questions) and 2) at least one time ''yes" in each risk of bias category (selection bias, information bias, confounding). A moderate risk of bias was defined as 1) ''yes" to at least 60% of the questions (5 out of 8 questions) and 2) at least one time ''yes" in two of the risk of bias categories. All other cases

were considered as high risk of bias. The two reviewers discussed their findings and asked a third reviewer for consensus, if necessary.

Data extraction

Data regarding study design, level of evidence, number of patients, population characteristics, arthroscopic findings, outcome measurements, results, and associated prognostic factors were extracted by one reviewer, using a standardized form.

Best evidence synthesis

The clinical and methodological homogeneity of the included studies was checked to evaluate whether a meta-analysis would be appropriate. If not, a Best Evidence Synthesis was performed, using the algorithm developed by van Tulder et al. [15-17]. By summarizing findings while taking the weight of the evidence into account in a standardized way, a Best Evidence Synthesis provides conclusions based on the best available evidence. The following ranking of levels of evidence was used: (1) Strong evidence is provided by two or more studies with low risk of bias and by generally consistent findings in all studies (≥75% of the studies reported consistent findings). (2) Moderate evidence is provided by one low risk of bias study and two or more moderate/high risk of bias studies or by two or more moderate/high risk of bias studies and by generally consistent findings in all studies (≥75%). (3) Limited evidence is provided by one or more moderate/high risk of bias studies or one low risk of bias study and by generally consistent findings (≥75%). (4) Conflicting evidence is provided by conflicting findings (<75% of the studies reported consistent findings). (5) No evidence is provided when no studies could be found. Besides overall analysis, subgroup analysis was performed regarding age (under- and above 45 years old).

RESULTS

Search strategy

We identified 5,150 potentially relevant articles: 5,146 by electronic search and 4 by reference tracking. After screening on title and abstract, 159 studies were considered to be potential eligible (See Figure 1). Full text of these studies was assessed, and 32 studies met our inclusion criteria and were included (See Table 1 for study characteristics and main results).

Characteristics of included studies

We included one randomized controlled trial [6], four prospective follow-up studies [18-21], and 27 retrospective studies. Overall, the included studies had allocated 4,250 patients (range 26 [22] – 1090 [23]). The follow-up ranged from 1 [6,19,23,24] to13 [25,26] year. The mean age of patients of the included studies ranged from 19 [26] to 60 [27] years. Most articles included patients

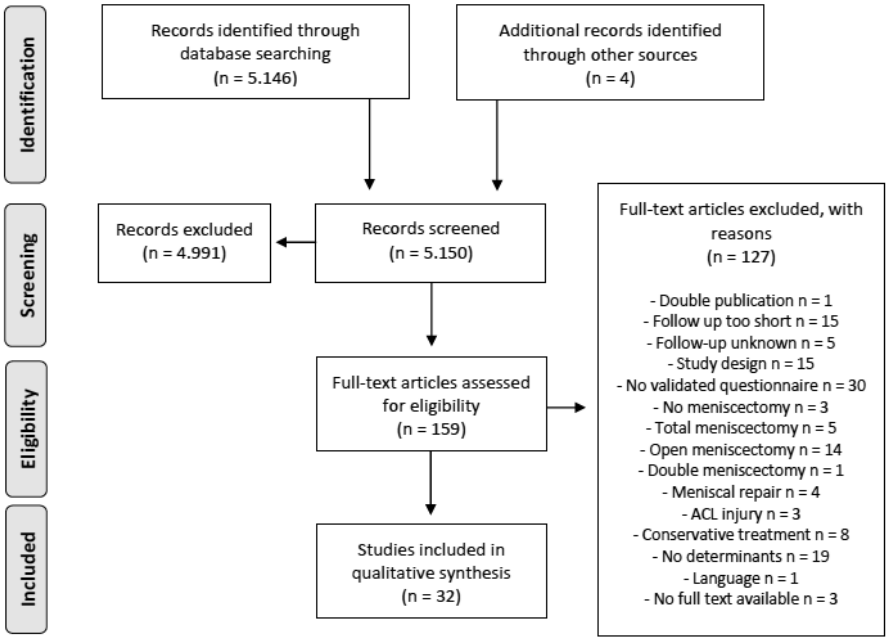

Figure 1. Flow-chart of screening and selection of studies. All steps were conducted according to the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA) statement.

with all types of meniscal tears, however two studies [28,29] only included radial tears, two studies [30,31] only horizontal tears, one study [32] only included root-tears, one study [33] only complex tears, and one study [34] only bucket-handle tears. Five studies excluded patients with a certain degree of chondral damage. Furthermore, 13 studies excluded patients with knee OA (mostly based on radiographs).

Risk of bias of included studies

For two [6,35] of the 32 included studies we found a low risk of bias. For the remaining studies, a moderate to high risk of bias was found. A risk of selection bias was found in 77% of the included studies, a risk of confounding in 94% and a risk of information bias in none of the studies. The agreement between reviewers in the risk of bias assessment was 98%.

Table 1. Study characteristics and main results of included studies

Author, Year of Publication	Study Design	Location: medial/lateral, Type of tear	Sample Size: N	Age: Yr. mean ± SD (range)	Follow-up: Yr. mean ± SD (range)	Female: N (%)	Risk of Bias (type of bias)	Independent variables	Outcome measure	Main conclusions (p-value)
Aune et al, 1995 [18]	Prospective cohort	Medial, all tear types	93	Median 45 (12-75)	3.5, SD: NM (2.1-4.2)	28 (30)	High (Sel., Conf.)	Chondral damage	Lysholm	Chondral damage: worse outcome ($p < 0.04$)
Bin et al, 2004 [19]	Retrospective cohort	Medial posterior horn, radial tears	85 (96 knees)	56, SD: NM (31-77)	2.3, SD: NM (1-4.3)	70 (73)	High (Sel., Conf.)	Tear depth	Lysholm	NS ($p > 0.05$)
Bin et al, 2008 [20]	Retrospective cohort	Medial, all tears	68	63, SD: NM (51-77)	4.3, SD: NM (3.1-6.9)	63 (93)	High (Sel., Conf.)	Location of chondral damage	Lysholm, VAS	NS ($p = 0.16$)
Bolano et al, 1993 [21]	Retrospective cohort	Medial and lateral, all tears	50	30, SD and range: NM	5.6, SD and range: NM	5 (10)	Moderate (Conf.)	Age, sex, duration of symptoms (</> 12 months), tear location/-type, chondral damage	Lysholm, Tegner	Higher age, long duration of symptoms, horizontal/ complex tear and chondral damage: worse outcome ($p < 0.05$) Sex, tear location: NS (p-value NM)
Bonneux et al, 2002 [22]	Retrospective cohort	Lateral, all tears	29 (31 knees)	25, SD and range: NM	8 ± 1.5 (range NM)	9 (36)	High (Sel., Conf.)	Sex, BMI, traumatic/non-traumatic, sport level, amount of resected tissue (subtotal/ limited)	IKDC, Lysholm	Larger amount of resected tissue (subtotal, >50%): worse outcome ($p = 0.02$) Sex, BMI, traumatic /non-traumatic, sport level: NS ($p = 0.3, 0.4, 0.2, 0.4$ resp.)
Chatain et al, 2003 [23]	Retrospective cohort	Medial and lateral, all tears	471	37 ± 12 (13-70)	11 ± 1.3 (10-15)	99 (21)	High (Sel., Conf.)	Age, sex, BMI, sport level, leg alignment, tear location (medial /lateral), tear type, chondral damage, amount of resected tissue (rim involved yes or no)	IKDC	Larger amount of resected tissue (rim involved): worse outcome ($p = 0.004$) Age, sex, BMI, sport level, leg alignment, tear location, -type, chondral damage: NS ($p \geq 0.05$)

Table 1. Study characteristics and main results of included studies

Author, Year of Publication	Study Design	Location: medial/lateral, Type of tear	Sample Size: N	Age: Yr. mean ± SD (range)	Follow-up: Yr. mean ± SD (range)	Female: N (%)	Risk of Bias (type of bias)	Independent variables	Outcome measure	Main conclusions (p-value)
Covall et al. 1992 [24]	Retrospective cohort	Medial and lateral, all tears	46 (56 knees)	57, SD: NM (45-72)	5.4 ± 1.3 (3-8)	6 (11)	High (Sel., Conf.)	Leg alignment, radiological knee OA	Modified Lysholm, Tegner	Radiological knee OA: worse outcome ($p < 0.05$) Valgus leg alignment: better outcome ($p < 0.001$)
Erdil et al, 2013 [25]	Retrospective cohort	Medial and lateral, all tears	1090	43, SD: NM (18-50)	1, SD and range: NM	423 (35)	Moderate (Conf.)	Sex, BMI, side of knee (left/right), tear type	IKDC, Lysholm, Oxford	Higher BMI: worse outcome ($p < 0.001$) Sex, side of knee, tear type: NS ($p = 0.88$ for sex, p-value for the others NM
Fauno et al, 1993 [26]	Retrospective cohort	Medial and lateral, all tears	88	30, SD: NM (13-62)	8.6 SD: NM (8-11.6)	24 (27)	Moderate (Conf.)	Age, sex, sport level, sport type, tear type, chondral damage	Lysholm	Higher age, ball sports, flap-tears: worse outcome ($p = 0.002$, 0.0001, 0.004 resp.) Sex, sport level, chondral damage: NS (p-value NM)
Ghislain et al, 2016 [27]	Retrospective cohort	Medial and lateral, all tears	117	47 ± 9 (18-72)	4 ± 0.3 (range NM)	69 (59)	High, (Sel., Conf.)	Traumatic/non-traumatic	Lysholm, SF-36	Non-traumatic: worse outcome ($p < 0.0001$)
Han et al, 2010 [28]	Retrospective cohort	Medial posterior horn, root tears	46	59, SD: NM (48-85)	6.5, SD: NM (5-8.6)	36 (78)	High, (Sel., Conf.)	Radiological knee OA, chondral damage	Lysholm	Radiological knee OA, chondral damage: worse outcome ($p = 0.004$, 0.002 resp.)
Haviv et al, 2015 [29]	Retrospective cohort	Medial, complex tears	135	51, SD: NM (20-80)	2, SD and range: NM	49 (36)	High, (Sel., Conf.)	BMI, chondral damage	Lysholm, VAS	Chondral damage: worse outcome in women ($p = 0.05$) Higher BMI: worse outcome in men ($p = 0.02$)
Haviv et al, 2016 [30]	Prospective cohort	Medial and lateral, all tears	201	44 ± 15 (range NM)	1 ± 0.3 (range NM)	68 (34)	High, (Sel., Conf.)	Age, sex, chondral damage	Lysholm, Tegner	Older age, female, chondral damage: worse outcome ($p < 0.0001$)
Haviv et al, 2016 [31]	Retrospective cohort	Medial and lateral, all tears	86	48 ± 13 (range NM)	1 ± 0.3 (range NM)	24 (28)	High, (Sel., Conf.)	Traumatic/non-traumatic	Lysholm, Tegner	Traumatic/non-traumatic: NS ($p = 0.24$)

Table 1. Study characteristics and main results of included studies

Author, Year of Publication	Study Design	Location: medial/lateral, Type of tear	Sample Size: N	Age: Yr. mean ± SD (range)	Follow-up: Yr. mean ± SD (range)	Female: N (%)	Risk of Bias (type of bias)	Independent variables	Outcome measure	Main conclusions (p-value)
Haviv et al, 2016 [32]	Retrospective cohort	Medial and lateral, all tears	187	46 ± 15 (range NM)	1 ± 0.3 (range NM)	51 (27)	High, (Sel., Conf.)	Duration of symptoms	Lysholm	Longer duration of symptoms: worse outcome (p = 0.01)
Hoser et al, 2001 [33]	Retrospective cohort	Lateral, all tears	29 (31 knees)	44 ± 13 (range NM)	10.3 ± 0.6 (9.2-12.1)	5 (17)	High, (Sel., Conf.)	Amount of resected tissue	Lysholm	Amount of resected tissue: NS (p-value NM)
Hulet et al, 2001 [34]	Retrospective cohort	Medial, all tears	57 (74 knees)	36 ± 11 (range NM)	12 ± 1 (range NM)	11 (19)	High, (Sel., Conf.)	Age, sex, traumatic/non-traumatic, activity, tear type, chondral damage	IKDC	Age, sex, traumatic/non-traumatic, activity, tear type, chondral damage: NS (p-value NM)
Hulet et al, 2015[35]	Retrospective cohort	Lateral, all tears	89	35 ± 13 (range NM)	22 ± 3 (range NM)	33 (37)	High, (Sel., Conf.)	Sex, tear type, amount of resected tissue	IKDC, KOOS	Larger amount of resected tissue: worse outcome (p-value NM) Sex, tear type: NS (p-value NM)
Jaureguito et al, 1995 [36]	Retrospective cohort	Lateral, all tears	26 (27 knees)	30, SD: NM (14-57)	8, SD: NM (5.5-11.3)	N.m.	High, (Sel., Conf.)	Age, leg alignment, tear type	Lysholm	Leg alignment, tear type, age: NS (p = 0.83, 0.45, NM resp.)
Kim et al, 2013 [37]	Retrospective cohort	Medial and lateral, horizontal tears	40	34, SD: NM (16-40)	2, SD and range: NM	24 (60)	Moderate (Conf.)	Traumatic/non-traumatic	IKDC, Lysholm	Traumatic/non-traumatic: N.S. (p = 0.41)
Kim et al, 2014 [38]	Retrospective cohort	Medial and lateral, all tears	312	41, SD: NM (13-62)	5, SD and range: NM	120 (38)	High (Sel., Conf.)	Amount of resected tissue (vertical resection/horizontal resection/subtotal	IKDC	Larger amount of resected tissue (subtotal): worse outcome (p < 0.001)
Kim et al, 2016 [39]	Retrospective cohort	Medial, horizontal tears	98 (100 knees)	40 ± 8 (range NM)	1.5 ± 1.5 range NM)	21 (21)	High (Sel., Conf.)	Tear type (direction)	IKDC, Tegner	Tear type: NS (p-value NM)

Table 1. Study characteristics and main results of included studies

Author, Year of Publication	Study Design	Location: medial/lateral, Type of tear	Sample Size: N	Age: Yr. mean ± SD (range)	Follow-up: Yr. mean ± SD (range)	Female: N (%)	Risk of Bias (type of bias)	Independent variables	Outcome measure	Main conclusions (p-value)
Maletius et al, 1996 [40]	Retrospective cohort	Medial and lateral, all tears	40	29, SD: NM (18-40)	13, SD: NM (12-15)	8 (20)	Low	Age, chondral damage	Lysholm, Tegner	Higher age: worse outcome (p = 0.03) Chondral damage: NS (p-value NM)
Menetrey et al, 2002 [41]	Retrospective cohort	Medial, all tears	32	60, SD: NM (51-74)	6, SD: NM (3-7)	11 (34)	High (Sel., Conf.)	Traumatic/non-traumatic	HSS Knee Score	Non-traumatic: worse outcome (p = 0.009)
Ozkoc et al, 2008 [42]	Retrospective cohort	Medial, radial root tears	67	56, SD: NM (38-70)	4.8, SD and range: NM	47 (70)	High (Sel., Conf.)	BMI	Lysholm	BMI: NS (p > 0.01)
Rockborn et al, 1995 [43]	Retrospective cohort	Medial and lateral, all tears	43	19, SD: NM (15-22)	13, SD: NM (11-15)	6 (14)	Moderate (Conf.)	Amount of resected tissue (partial/ subtotal)	Lysholm, Tegner	Larger amount of resected tissue (subtotal): worse outcome (p = 0.02)
Rosenberger et al, 2010 [44]	Prospective cohort	Medial and lateral, all tears	180	48, SD: NM (17-78)	1, SD and range: NM	79 (44)	High (Sel., Conf.)	Age, sex, BMI, activity, fitness, prior injury, chondral damage	Lysholm, Tegner	Female, lower fitness, prior injury, chondral damage: worse outcome (p = 0.0001, 0.033, 0.002, 0.028 resp.) Age, BMI, activity: NS (p = 0.32, 0.20, 0.42 resp.)
Scanzello et al, 2013 [45]	Prospective cohort	Medial and lateral, all tears	33	Median 45 (IQR 40-53)	2, SD and range: NM	12 (36)	High (Sel., Conf.)	Synovial inflammation	Lysholm	Synovial inflammation: NS (p = 0.14)
Scheller et al, 2001 [46]	Retrospective cohort	Lateral, all tears	75	41, SD and range: NM	9.5, SD: NM (5-15)	32 (42)	High, (Sel., Conf.)	Age, BMI, traumatic/non-traumatic, tear type	Lysholm	Higher age and higher BMI: worse outcome (p-value NM) Traumatic/non-traumatic, tear type: NS (p-value NM)
Shelbourne et al, 2006 [47]	Retrospective cohort	Medial, bucket-handle tears	79	29 ± 11 (13-57)	11.8 ± 6.9 (3-22)	4 (5)	High (Sel., Conf.)	Age	IKDC	Age: NS (R^2 = -0.33)

Table 1. Study characteristics and main results of included studies

Author, Year of Publication	Study Design	Location: medial/lateral, Type of tear	Sample Size: N	Age: Yr. mean ± SD (range)	Follow-up: Yr. mean ± SD (range)	Female: N (%)	Risk of Bias (type of bias)	Independent variables	Outcome measure	Main conclusions (p-value)
Sihvonen et al 2013 [6]	Prospective randomized controlled trial	Medial, all tears	146	52 ± 7 (range NM)	1	57 (39)	Low	Traumatic/non-traumatic	Lysholm, WOMET	Traumatic/non-traumatic: NS (p-value NM)
Yilar et al, 2014 [48]	Retrospective cohort	Medial and lateral, all tears	90	58 ± 9 (38-82)	12, SD and range: NM	64 (71)	High, (Sel., Conf.)	Age, sex, BMI (BMI <25/25-29/>29)	Lysholm, WOMAC	Higher BMI (>29): worse outcome ($p < 0.0001$) Age, sex: NS (p-value NM)

Abbreviations: NS = no statistically significant difference found. NM = not mentioned. Sel. = Selection bias, Conf. = Confounding. IQR = Inter-Quartile Range. IKDC = International Knee Documentation Committee. KOOS = Knee injury and Osteoarthritis Outcome Score. VAS = Visual Analogue Scale. HSS Knee Score = Hospital for Special Surgery Knee Score. SF-36 = Short Form health survey. WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index. WOMET = Western Ontario Meniscal Evaluation Tool

Heterogeneity

A significant amount of variety was found between included studies regarding study-population, the definition of subgroups, and outcome measures. Furthermore, clinical outcomes of individual subgroups were often inadequately described or lacking completely. Taking the considerable heterogeneity and lacking subgroup-outcomes into account, pooling data and conducting a meta-analysis was not appropriate. Hence, qualitative analyses were performed, according to the Best Evidence Synthesis principle.

Prognostic factors

In total, 13 different prognostic factors were identified and shown to be associated with clinical outcome following APM. Table 2 shows an overview of prognostic factors, which are described in at least two studies.

1) MODERATE EVIDENCE

Prognostic factors:

Duration of symptoms

Two studies [36,37] evaluated the duration of symptoms in the context of clinical outcome. In one study [36] acute (symptoms existing less than 12 months) and chronic (symptoms existing more than 12 months) lesions are distinguished, one study [37] defined a duration of three months or less as ''short", and longer than three months as ''long'". Both studies concluded that a shorter duration of symptoms is statistically significantly associated with better patient reported outcome measures.

Radiological knee OA at baseline

Two studies [38,39] described the presence of radiological knee OA and its association with clinical outcome of APM. In one study [39], patients with no sign of knee OA (Kellgren and Lawrence [40] grade 0) and patients with mild to moderate knee OA (Kellgren and Lawrence grade 1-2) were included. One study [38], also included patients with severe knee OA (Fairbank [41] grade > 2). Both studies reported a statistically significant smaller improvement of Lysholm knee scores in patients with radiological knee OA at baseline.

Amount of resected meniscal tissue

Six studies assessed the relationship between the amount of resected tissue during APM and clinical outcome. Five out of six studies reported a positive association between the amount of resected meniscal tissue and decreased patient reported outcome measures. In two studies [26,42], a ''subtotal" procedure (more than 50% resected, leaving a small rim of meniscal tissue) was found to result in worse clinical outcome than a ''partial" procedure (less

Table 2. Infuence of determinants on worse clinical outcome after APM					
Group	**Determinants**	**No. of studies**	**Associated with worse outcome LR/MR/HR: n studies**	**No significant relationship LR/MR/HR: n studies**	**Best-evidence-synthesis**
Patient-related factors	Older age at baseline	11	LR: 1[40] MR: 2[21 26] HR: 2[30 46]	HR: 6[23 34 44 48 50]	Conflicting Evidence
	Female sex	10	HR: 2[30 44]	MR: 3[21 25 26] HR: 5[22 23 34 35 48]	Moderate Evidence
	Higher BMI	7	MR: 1[25] HR: 3[29 46 48]	HR: 3[22 42 44]	Conflicting Evidence
	Longer duration of symptoms	2	MR: 2[21] HR: 1[32]		Moderate Evidence
	Non-traumatic onset	8	HR: 2[27 41]	LR: 1[6] MR: 1[37] HR: 4[22 31 34 46]	Moderate Evidence
	Lower pre-operative sport level	4		MR: 1[26] HR: 3[22 23 44]	Moderate Evidence
	Leg malalignment	3	HR: 1[24]	HR: 2[23 50]	Conflicting Evidence
Intra-articular factors	Type of meniscal tear	9	Deg/ complex tear: MR: 1[21] Flap tear: MR: 1[26]	HR: 7[23 25 34 35 39 46 50]	Moderate Evidence
	Radiological knee OA at baseline	2	HR: 2[24 28]		Moderate Evidence
	Chondral damage during arthroscopy	10	MR: 1[21] HR: 5[28-30 44 53]	LR: 1[40] MR: 1[26] HR: 2[23 34]	Conflicting Evidence
	Resecting more tissue	6	MR: 2[38 43] HR: 3[22 23 35]	HR: 1[33]	Moderate Evidence

Abbreviations: APM = arthroscopic partial meniscectomy, LR = Low Risk of Bias, MR = Moderate Risk of Bias, HR = High Risk of Bias, OA = osteoarthritis, deg = degenerative, BMI = body mass index

than 50% of meniscal tissue resected). Other studies described the absence of the meniscal rim [43] or a preserved meniscal width of less than 3 mm [44] as a predictor for worse clinical outcome. In one study [45], the method for measuring the influence of this factor on clinical outcome was not further described. One study [46], which investigated the influence of the

percentage of removed tissue in 31 knees with lateral meniscal tears, found no association with post-operative Lysholm scores.

Not prognostic factors:

Sex

The influence of sex on outcome after APM was assessed in ten articles. Eight of them reported no statistically significant association between sex and outcome. Two studies [19,21] reported a worse outcome for women.

Traumatic versus degenerative tear

The influence of onset, i.e. traumatic versus degenerative, on outcome after APM was assessed in eight articles and seemed not to be a predictor for clinical outcome. Two studies [27,47] reported a worse outcome for degenerative tears, based on arthroscopic findings. However, six studies reported no statistically significant correlation.

Pre-operative sport level

In four studies preoperative sport level was assessed. Two studies [42,43] distinguished a recreational and competitive sport level, one study [19] measured the hours of exercise per week and one study [48] did not further specify study groups. None of the articles found a correlation between sport level and outcome of APM.

Type of meniscal tear

In nine studies the association between the type of meniscal tear and clinical outcome was assessed. Eight of them found no association, whereas one study [36] reported a worse outcome for complex and for degenerative tears. None of the studies described a classification system used for the type of meniscal tears. Furthermore, a large variety among studies was found regarding the definition of subgroups (types of meniscal tears). The amount of subgroups ranged from two [36,48] to five [23].

2) LIMITED EVIDENCE

An association between the location of the tear (medial versus lateral meniscus) and clinical outcome of APM was only described in one of our included studies [43]; in this study no statistically significant difference was found between medial and lateral APMs. Regarding the side of knee [23], the location of chondral damage [49] and perioperative synovial inflammation [20], no correlation with clinical outcome was found as well. Furthermore, one of the included studies [19] assessed the predictive value of self-reported fitness at baseline and prior knee surgery and found a worse Lysholm score one year after APM for women with lower self-reported fitness.

For men, no influence was found of self-reported fitness on clinical outcome. Prior knee injury resulted in a lower Lysholm after APM in women, in men however no such association was found.

3) CONFLICTING EVIDENCE

Age at baseline

The influence of age on clinical outcome following APM was investigated in 11 studies. In two studies [25,48], patients were divided into two groups; under 30 years old and above 30 years old. One article [36] divided patients in a group under and above 40 years. In the remaining studies, the method for defining age subgroups was not specified. Five studies found a worse clinical outcome for older patients, and six studies did not find a statistically significant association.

Body Mass Index

Seven studies described the association between Body Mass Index (BMI) and clinical outcome. Four of them reported a worse Lysholm score for overweight or obese patients. The remaining studies found no association between BMI and clinical outcome. When we looked at studies with patients above 45 years old, we found evidence for the fact that there is no association between BMI and clinical outcome of APM.

Leg malalignment

The predictive value of leg malalignment was described in three studies. One of them [38] reported a statistical significantly worse Modified Lysholm score for patients with a valgus malalignment (tibiofemoral angle more than 4 degrees on anteroposterior full leg radiograph). However, two studies [22,43] found no significant association between leg malalignment and outcome.

Chondral damage during arthroscopy

Ten studies investigated the association between chondral damage found during surgery and clinical outcome. Three of them used the Outerbridge [50] classification, two of them the ICRS (International Cartilage Repair Society [51]) classification, and the remaining studies only mentioned whether chondral damage was found during arthroscopy or not. Six out of ten studies reported that the presence of chondral damage predicted a worse clinical outcome, and four studies did not find such an association. The relationship between chondral damage and clinical outcome seems to be driven by age; when we looked at studies with patients above 45 years old (n = 4), all studies reported a worse outcome for patients with chondral damage during arthroscopy. Looking at studies with patients below 45 years old (n = 6),

almost all studies reported no association between chondral damage and outcome. Furthermore, when specifically looking at medial meniscal tears, chondral damage seems to be a prognostic factor for worse outcome as well.

DISCUSSION

Despite the extensive heterogeneity in study design, in the definition of subgroups and in outcome measurements, several prognostic factors were found for the clinical outcome after APM. We found moderate evidence that a larger amount of resected tissue, the presence of radiological knee OA at baseline, and a longer duration of complaints are associated with a worse clinical outcome following APM. Sex, the preoperative sport level, onset (traumatic versus degenerative), and the type of meniscal tear do not seem to influence clinical outcome. It should be noted that, the phrasing ''worse outcome" does not necessarily mean that the outcome is unsatisfactory. It means that, having a specific factor is associated with a worse patient-reported outcome compared to not having this specific factor.

To the best of our knowledge, this is the first systematic review that focuses specifically on predictors for the clinical outcome following APM. Salata and colleagues [52] conducted a systematic review in 2010 on the radiological and clinical outcome in patients undergoing meniscectomy. The authors primarily assessed outcome measurements of APM in general, but also described some features which might influence this outcome. One of their outcomes was, that degenerative meniscal tears are statistically significant associated with a negative postoperative outcome. This is a very relevant finding, as most APMs are performed in middle-aged and elderly patients, who typically have degenerative meniscal tears [5,53-55]. The findings of Salata are in concordance with Englund et al. [56], who found that degenerative meniscal tears result in worse clinical and radiological outcome after 16 years in 155 patients undergoing APM. By contrast, a recently published and methodologically robust study of Thorlund et al. [57]. reported no clinically relevant difference in patient reported knee function and –satisfaction between degenerative and traumatic meniscal tears after 12 months. This is in line with the results of the current systematic review, in which no difference in patient reported clinical outcome between degenerative and traumatic tears was found as well. Thus, the predictive value of degenerative versus traumatic meniscal tears for the clinical outcome following APM is questionable and needs to be further unraveled.

A factor that does seem to influence clinical outcome following APM, is the duration of symptoms. Although a short duration of symptoms (less than six weeks) is one of the clinical variables that orthopedic surgeons consider to be important in surgical decision making [58], robust evidence regarding the impact of timing awaiting for APM on clinical outcome is scarce. The fact that there is no standard definition of ''acute" and ''chronic" symptoms

causes a substantial amount of heterogeneity between studies, which makes them difficult to compare. Nonetheless, in the present systematic review, moderate evidence was found that a longer duration of symptoms (longer than 3-12 months) is associated with a worse clinical outcome following APM.

A third key-finding concerns the amount of resected meniscal tissue during arthroscopy, which appeared to be a relevant factor in predicting the clinical outcome following APM. This is not surprising, given the critical biomechanical role of the meniscus within the knee joint [59]. Our study suggests that the amount of resected meniscal tissue is negatively associated with postoperative clinical outcome following APM, in concordance with Englund [56] and Salata [52]. More specifically, resecting more than 50% of meniscal tissue, leaving less than 3 mm meniscal width and impairing the peripheral third (the meniscal rim) were found to be associated with worse clinical outcome. In conclusion, resecting more meniscal tissue is associated with worse clinical outcome after APM.

Whereas no association was found between degenerative meniscal tears (compared to traumatic tears) and a worse clinical outcome following APM, our study does show that radiological knee OA at baseline is associated with a worse clinical outcome. This is in line with the results of Kirkley and colleagues [60], showing that arthroscopic surgery for patients suffering knee OA, may not lead to satisfactory outcomes. The interesting thing is that a degenerative meniscal tear, as described earlier, does not seem to be associated with a worse clinical outcome following APM. As degenerative meniscal tears are often considered to be a signifying feature of incipient knee OA [61-63], one might expect that this type of tear, compared to traumatic meniscal tears, has a negative association with clinical outcome as well. Further investigation into this topic, for example using novel imaging techniques which provide quantitative information regarding the degree of meniscal degeneration [64], is desired.

Another relevant knee-specific factor that we studied, is chondral damage during surgery. Symptomatic degenerative meniscal tears are frequently associated with cartilage damage to the corresponding articular surfaces [65,66]. In the current systematic review, conflicting evidence was found for the predictive value of chondral damage on clinical outcome after APM.. However, subgroup analysis showed that, when looking at the studies in patients with a mean age of < 45 years, no association was found between chondral damage and outcome. For the studies in patients with a mean age of > 45 years, we did find that chondral damage at time of surgery is associated with a worse clinical outcome. A study by Sofu et al. [67], in which patients above 60 years old with traumatic meniscal tears were included, reported worse pain scores for patients with chondral damage as well. Thus, it is likely that chondral damage in patients aged above 45 years has a negative influence on clinical outcome following APM, however this association needs to be further investigated.

Another factor that could potential be of influence on clinical outcome, is whether the tear is located in the lateral- or the medial meniscus. However, this factor was studied in only

one of the included publications, which did not find an association. As a potential prognostic factor needs to be described in at least two studies, according to the Best Evidence Syntheses principle, no conclusions regarding the predictive value of medial versus lateral meniscectomies can be drawn. This factor is particularly relevant as in literature, lateral meniscectomy has been reported to result in poorer postoperative outcome than medial meniscectomy [52,68-70]. A hypothesis is that the lateral meniscus is ''less conforming" than the medial meniscus after meniscectomy, resulting in an increased amount of instability and resultant force transmission to the articular cartilage. By all means, the predictive value of this factor too warrants further investigation.

A major strength of the present study is that we performed an extensive search in all relevant databases by aid of an experienced biomedical information specialist of the medical library of our institution. Furthermore, all steps in this systematic review were performed in duplo and acknowledged tools for the assessment of the risk of bias and data extraction were used. A limitation of our systematic review is that, despite the large amount of found publications, relatively few studies could be included in this systematic review. This is a consequence of our selection strategy, involving extensive exclusion criteria. To increase the a priori chance of acquiring reliable and comparable results (and potential conduct a meta-analysis) we defined concrete, well justified and clearly stated eligibility criteria. For example, we only included articles using validated questionnaires, such as the Lysholm- or IKDC (*International Knee Documentation Committee*[71]) score. Publications using outcome measures such as ''percentage of satisfied patients" were therefore excluded. The rationale of this exclusion criterion is the relatively low reliability and reproducibility of non-validated patient reported outcome measurements. Although we might have missed information about prognostic factors, we believe that this approach increased the reliability of our results.

Another limitation of this systematic review is, that only rough estimations of the effect size of the found prognostic factors could be provided. This is due to the fact that a substantial amount of heterogeneity in the definition of subgroups and outcome measurements was found. For example, the potential influence of the type of meniscal tear on clinical outcome following APM was reported in nine studies, however none of them described a classification system for the type of tear. In fact, six of them did not provide any information regarding the definition of meniscal tear subgroups at all. Also, in many of the included studies the outcome of subgroups was poorly described. Often only P values were reported; some studies did not even provide a P value but only described the prognostic value of a specific factor (e.g. ''No significant correlation was found between the amount of tissue resected and the subjective, clinical and radiological outcome" [46]). Given the found heterogeneity and inadequately described subgroup results, pooling of study results and performing a meta-analysis were not justified. This implied that small studies might not have reported an association

based on lower power while pooled results the reported association would have counted in the overall estimation for the association.

Despite the high amount of APMs performed worldwide, there is a lack of consensus on the indications for this procedure, particularly in younger and middle-aged patients. To enable a more evidence-based approach in surgical decision making, knowledge of the predictive value of certain patient-specific factors for the clinical outcome is essential. In this comprehensive systematic review, prognostic factors for the patient-reported outcome of APM were assessed. We have shown that, based on the best available evidence, radiographic knee OA at baseline, a long duration of complaints, and resecting more meniscal tissue during arthroscopy are associated with a worse postoperative clinical outcome. The findings could contribute to the development of a prediction model for the clinical outcome of APM, based on patient-specific factors, which could guide orthopedic surgeons in their clinical decision making. However, within the available literature, the earlier mentioned heterogeneity and inadequately reported subgroup outcomes make it challenging to draw adequate conclusions. Therefore, there is an urgent need for more well-designed, robust clinical trials on arthroscopic meniscal surgery using validated patient reported outcome measurements and with relevant, a priori defined subgroups.

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SUPPLEMENTARY MATERIAL 1: COMPLETE SEARCH

Database:	Original hits:	Without duplicates:
Embase.com	3630	3554
Medline (OvidSP)	3179	806
Web-of-science	1231	363
Cochrane	181	3
SPORTDiscus (Ebsco)	620	79
Google Scholar	200	59
Total	9041	4864

Embase.com:

('knee meniscus rupture'/de OR ('knee meniscus'/de AND (rupture/exp OR 'knee injury'/exp)) OR meniscectomy/de OR ((menisc* NEAR/6 (tear* OR rupture* OR injur* OR lesion* OR damage* OR trauma* OR torn)) OR meniscopath* OR meniscectom*):ab,ti) AND (therapy/exp OR 'treatment outcome'/exp OR exercise/exp OR surgery/exp OR arthroscopy OR rehabilitation/exp OR therapy:lnk OR rehabilitation:lnk OR surgery:lnk OR (therap* OR treat* OR conservativ* OR physiotherap* OR kinesiotherap* OR kinesitherap* OR exercise* OR surg* OR nonsurg* OR postsurg* OR meniscectom* OR remov* OR resect* OR operati* OR postoperati* OR nonoperati* OR rehabilitat*):ab,ti) AND (prognosis/de OR 'follow up'/de OR 'cohort analysis'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR (prognos* OR 'follow up' OR followup OR cohort* OR longitudinal OR retrospective OR prospective OR 'long term' OR 'medium term' OR 'late results'):ab,ti) NOT ([animals]/lim NOT [humans]/lim)

Medline (OvidSP):

(Menisci, Tibial/in OR ("Menisci, Tibial"/ AND (rupture/ OR "Knee Injuries"/)) OR ((menisc* ADJ6 (tear* OR rupture* OR injur* OR lesion* OR damage* OR trauma* OR torn)) OR meniscopath* OR meniscectom* OR arthroscopy).ab,ti.) AND (exp therapeutics/ OR exp "treatment outcome"/ OR exp exercise/ OR exp "Surgical Procedures, Operative"/ OR exp rehabilitation/ OR rehabilitation.xs. OR therapy.xs. OR surgery.xs. OR (therap* OR treat* OR conservativ* OR physiotherap* OR kinesiotherap* OR kinesitherap* OR exercise* OR surg* OR nonsurg* OR postsurg* OR meniscectom* OR remov* OR resect* OR operati* OR postoperati* OR nonoperati* OR rehabilitat*).ab,ti.) AND (prognosis/ OR exp "cohort studies"/ OR (prognos* OR "follow up" OR followup OR cohort* OR longitudinal OR retrospective OR prospective OR "long term" OR "medium term" OR "late results").ab,ti.) NOT (exp animals/ NOT humans/)

Cochrane:

(((menisc* NEAR/6 (tear* OR rupture* OR injur* OR lesion* OR damage* OR trauma* OR torn)) OR meniscopath* OR meniscectom*):ab,ti) AND ((therap* OR treat* OR conservativ* OR physiotherap* OR kinesiotherap* OR kinesitherap* OR exercise* OR surg* OR arthroscopy OR nonsurg* OR postsurg* OR meniscectom* OR remov* OR resect* OR operati* OR postoperati* OR nonoperati* OR rehabilitat*):ab,ti) AND ((prognos* OR 'follow up' OR followup OR cohort* OR longitudinal OR retrospective OR prospective OR 'long term' OR 'medium term' OR 'late results'):ab,ti)

Web-of-science:

TS=((((menisc* NEAR/6 (tear* OR rupture* OR injur* OR lesion* OR damage* OR trauma* OR torn)) OR meniscopath* OR meniscectom*)) AND ((therap* OR treat* OR conservativ* OR physiotherap* OR kinesiotherap* OR kinesitherap* OR exercise* OR surg* OR arthroscopy OR nonsurg* OR postsurg* OR meniscectom* OR remov* OR resect* OR operati* OR postoperati* OR nonoperati* OR rehabilitat*)) AND ((prognos* OR "follow up" OR followup OR cohort* OR longitudinal OR retrospective OR prospective OR "long term" OR "medium term" OR "late results")) NOT ((animal* OR rabbit* OR mouse OR mice OR rat OR rats OR canine OR dog OR dogs OR sheep OR cat OR cats OR horse* OR bovine OR goat* OR porcine* OR pig OR swine) NOT (human* OR patient*)))

SPORTDiscus (Ebsco):

(DE "meniscus (Anatomy) - Wounds & injuries" OR ((menisc* N6 (tear* OR rupture* OR injur* OR lesion* OR damage* OR trauma* OR torn)) OR meniscopath* OR meniscectom*)) AND (DE therapeutics+ OR DE "treatment outcomes+" OR DE exercise+ OR DE "OPERATIVE surgery+" OR DE rehabilitation+ OR (therap* OR treat* OR conservativ* OR physiotherap* OR kinesiotherap* OR kinesitherap* OR exercise* OR surg* OR arthroscopy OR nonsurg* OR postsurg* OR meniscectom* OR remov* OR resect* OR operati* OR postoperati* OR nonoperati* OR rehabilitat*)) AND (DE "cohort analysis+" OR (prognos* OR "follow up" OR followup OR cohort* OR longitudinal OR retrospective OR prospective OR "long term" OR "medium term" OR "late results")) NOT (DE animals+ NOT DE humans)

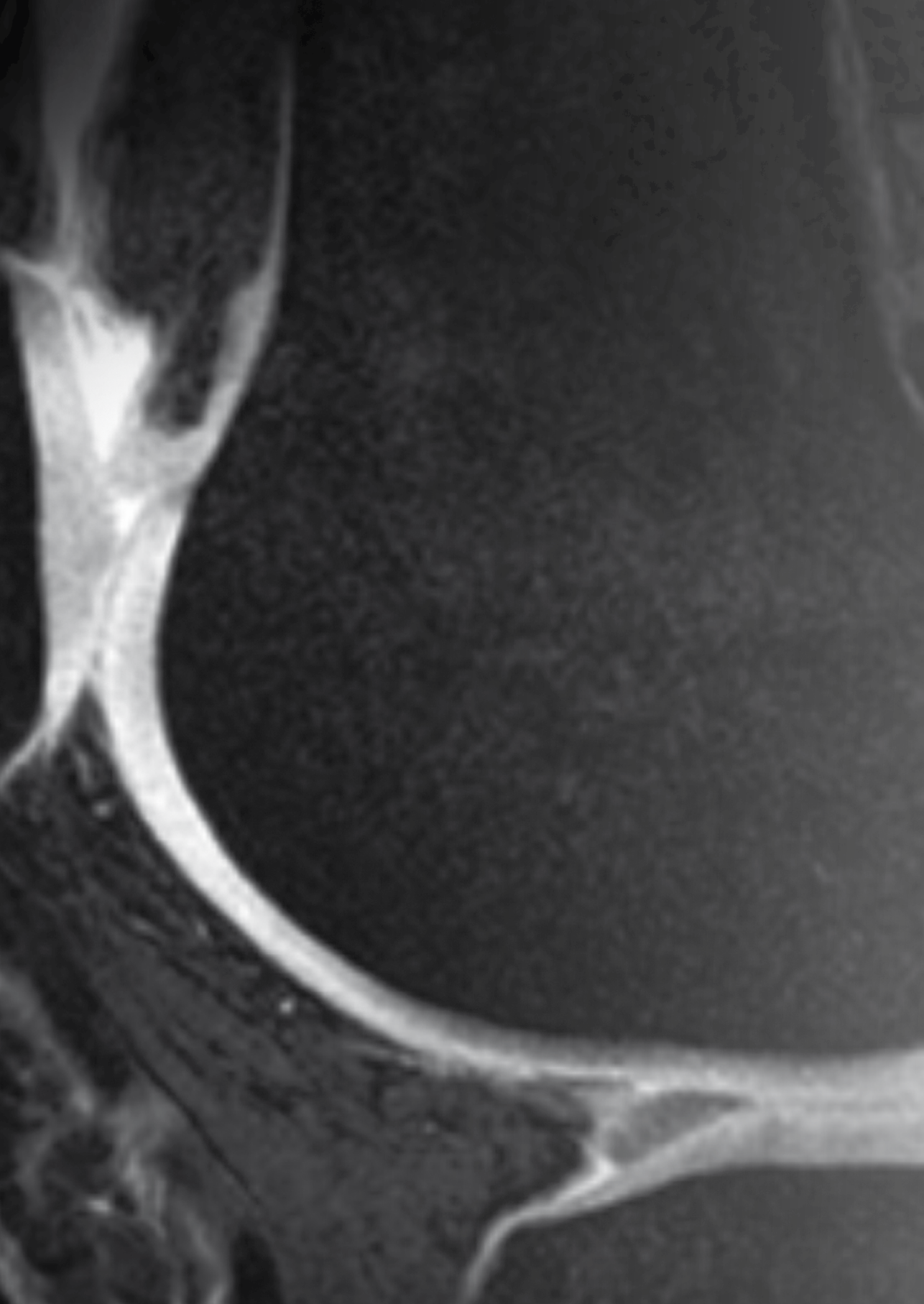
PubMed publisher:

(((menisc*[tiab] AND (tear*[tiab] OR rupture*[tiab] OR injur*[tiab] OR lesion*[tiab] OR damage*[tiab] OR trauma*[tiab] OR torn)) OR meniscopath*[tiab] OR meniscectom*[tiab])) AND ((therap*[tiab] OR treat*[tiab] OR conservativ*[tiab] OR physiotherap*[tiab] OR kinesiotherap*[tiab] OR kinesitherap*[tiab] OR exercise*[tiab] OR arthroscopy OR surg*[tiab] OR nonsurg*[tiab] OR postsurg*[tiab] OR meniscectom*[tiab] OR remov*[tiab] OR resect*[tiab] OR operati*[tiab] OR postoperati*[tiab] OR nonoperati*[tiab] OR rehabilitat*[tiab])) AND ((prognos*[tiab] OR follow up*[tiab] OR followup[tiab] OR cohort*[tiab] OR longitudinal[tiab]

OR retrospective[tiab] OR prospective[tiab] OR long term*[tiab] OR medium term*[tiab] OR late result*[tiab])) AND publisher[sb]

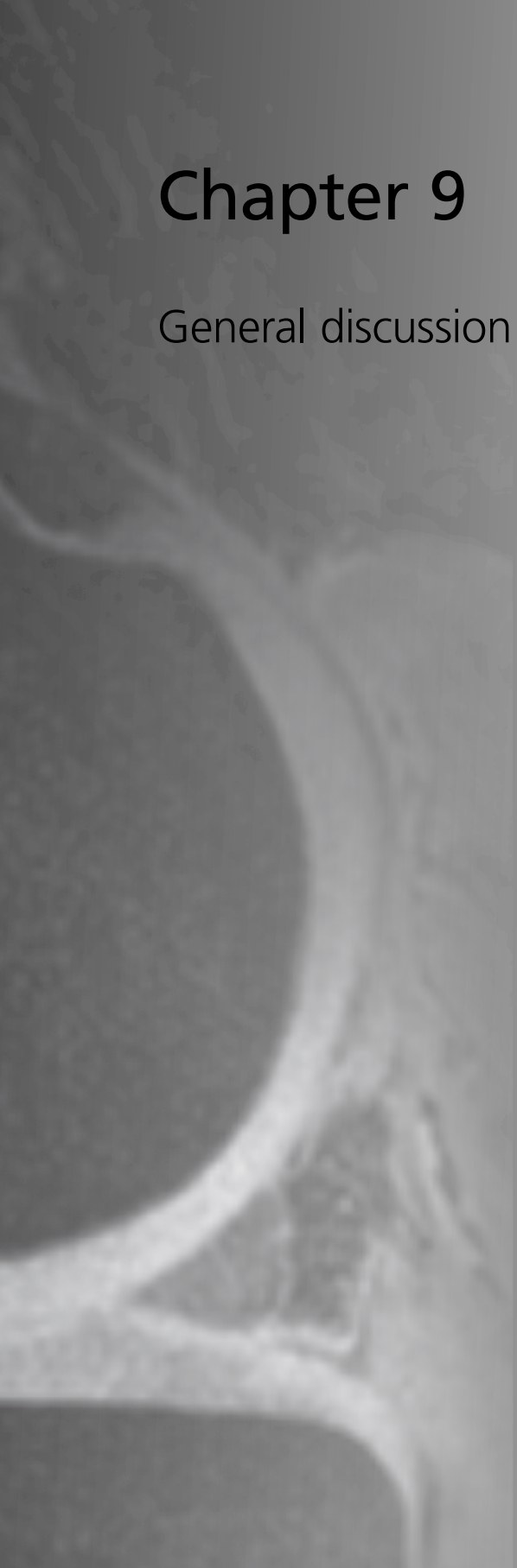
Google scholar:

"meniscus|meniscal tear|rupture|ruptures|injury|lesions|trauma" therapy|treatment|exercise|surgery|therapuetic|rehabilitation|surgery|arthroscopy|surgical|meniscectomy|operative prognosis|"follow up"|cohort|longitudinal|retrospective|prospective|"long|medium term"



Chapter 9

General discussion



PART I: IMAGING OF MENISCAL PATHOLOGY

Advances in MRI techniques have made great progress in recent years, providing new and better ways of visualizing meniscal pathologies. In particular, quantitative MRI (qMRI) techniques, such as T_2 mapping are promising in musculoskeletal research. These techniques have the capacity to non-invasively show subtle changes in biochemical tissue composition and open the door to early stage detection of meniscal degeneration, knee OA and other joint pathologies [1-6]. T_2 mapping and other advanced MRI techniques have a tremendous potential in musculoskeletal imaging, however the usefulness of these techniques in clinical practice and implications for further treatment depends on their validity, reproducibility, responsiveness, and feasibility. The general aim of Part I of this thesis is to gain more insight into these features; they will be discussed in more detail in the next paragraphs.

Validity of T_2 mapping for meniscus

In musculoskeletal imaging, T_2 mapping was originally developed for articular cartilage [2,7,8]. Consequently, this technique has become widely studied to quantitatively assess cartilage degeneration. A recent systematic review on articular cartilage qMRI techniques reported good to excellent reproducibility and discriminative validity to distinguish degree of degeneration for T_2 mapping [4]. T_2 mapping of the meniscus is relatively new [9-11]. As a result of its tightly organized collagen structure, the meniscus has relatively shorter T_2 components than those of cartilage, resulting in lower T_2 relaxation times. The T_2 relaxation time (in this thesis referred to as "T_2 value") of certain tissue represents the time protons take to return to their original (i.e., resting) state. Meniscal T_2 relaxation times of healthy subjects are around 11 ms [11,12]; at the bottom end of the range of echo time values in standard spin echo based T_2 mapping sequences in musculoskeletal research (often ranging from 10-100 ms) [6]. Due to the short T_2, and the heterogeneity of meniscal tissue, concerns have been raised in previous studies that standard spin echo based T_2 mapping is not suitable to measure T_2 of the meniscus [13-17].

These concerns were addressed in a study by Nebelung et al., who validated several meniscal qMRI techniques (including T_2 mapping) with histology [9]; the gold standard for tissue changes. For T_2 mapping, the authors reported a correlation coefficient of 0.65. It should be noted, however, that T_2 measurements were performed *ex vivo*. That is, T_2 mapping was performed after the menisci were removed from the knee. During *ex vivo* experiments, meniscal T_2 relaxation times may be influenced by storage processes (e.g., alterations in tissue hydration) [9,10] or the temperature in the scanning room (usually room temperature instead of body temperature) [9]. *Ex vivo* studies may therefore result in a lower value of correlation. Moreover, in the study by Nebelung et al., the authors pointed out that T_2 sequence parameters used in their study (e.g., echo time values started at 10.4 ms), might not have been optimal for meniscal T_2 measurements, which is understandable given the broad range of qMRI outcome parameters they measured.

To overcome these limitations, we performed an *in vivo* meniscal T_2 mapping validation study. To our knowledge, this study, described in **Chapter 2**, is the first to assess meniscal T_2 mapping *in vivo* against histology. We prospectively assessed meniscal tissue, obtained during total knee replacement surgery from patients with knee OA, and found a strong correlation (R = 0.86) between T_2 values and histological grade of degeneration. Although these results must be interpreted with care given the relatively small sample size (21 meniscal regions from 13 menisci), these findings do suggest that meniscal T_2 measurements are accurate using standard spin echo based T_2 mapping. It should be noted that great care must be taken when choosing MRI sequence parameters, especially regarding echo time values. Preferably, one should use echo time values starting relatively low (< 5 ms).

We have to point out that our validation study was performed only in OA patients, and these findings might not be applicable in the same way across other patient groups. In future research, validation of *in vivo* meniscal T_2 mapping in other patient groups is needed. We are currently collecting data (MRI and histology) of patients with traumatic meniscal tears (e.g., STARR trial patients). Preliminary results (not yet published) suggest a strong correlation between T_2 measurements and histological degree of degeneration in the retrieved menisci of these patients. An important challenge in this context lies in the image post processing and analysis of T_2 mapping, in particular, the question of exactly how to handle meniscal tears in segmentation. It seems logical to exclude the actual tear while segmenting the meniscus, as that specific area on MRI does not represent meniscal tissue. However, it needs to be acknowledged that potential bias can occur because of misinterpretation of meniscal tears due to anatomic variants, artefacts, post-traumatic changes, or post-surgical meniscal changes (i.e., after APM) [18-20]. The latter factor, meniscal changes after APM, is particularly relevant given the tremendous number of APMs performed worldwide [21,22].

Another limitation of our validation study is the lack of zonal differentiation, for instance between radially inner (often called white) and outer (often called red) zones and between deep and superficial zones. Although no consensus exists regarding the exact pattern, several studies have reported that there are regional differences regarding meniscal tissue composition and biomechanical properties [10,13,23]. Our study results provide an overall estimation of good accuracy for meniscal T_2 mapping, although findings may not be representative for meniscal subregions. The rationale behind our approach was that the Pauli score (which we used for histological grading) does not distinguish meniscal zones, and, accordingly, the entire cross-section needs to be assessed [24]. Hence, a separate score for different meniscal zones was not possible. Future studies should be performed to evaluate the diagnostic performance of meniscal T_2 mapping in different zones [25]. Also, given the fairly large number of different qMRI methods available (compositional techniques such as T_2 mapping and $T_1\rho$ as well as measures for volume and thickness [9,11,26,27]), the research community should strive for

a standardized algorithm regarding the application of these techniques in musculoskeletal research.

Reproducibility of T_2 mapping in a multicenter setting

In the STARR trial, T_2 mapping is used as outcome measure for early cartilage degeneration two years after meniscal injury. In such a multicenter study, knowledge of reproducibility of T_2 measurements is critical. Two aspects of reproducibility are relevant in this setting: 1) longitudinal reproducibility of T_2 measurements and 2) cross-validation of T_2 values across centers.

1) Longitudinal reproducibility (sometimes referred to as repeatability or test-retest) of T_2 measurements is crucial for distinguishing between true T_2 changes and random error. In general, a good to excellent longitudinal reproducibility is reported for cartilage T_2 mapping [4,28,29]. The majority of reports in this context, however, are single-site studies. Few studies have assessed longitudinal reproducibility of cartilage T_2 mapping in a multicenter setting [4]; generally using a single type of MRI scanner and harmonized acquisition protocols. This approach is optimal from an imaging perspective and provides valuable information for future use of T_2 mapping. However, one should realize that often various scanner types are present when performing a multicenter study, similar to clinical practice. In the STARR trial, for instance, various types of MRI scanners are present in the participating centers. Moreover, local requirements and restrictions regarding MRI acquisition in participating centers may prevail over optimal imaging strategy, especially in large multidisciplinary clinical trials, in particular regarding scan time. All these factors emphasize the importance of evaluating longitudinal reproducibility of T_2 mapping in a multivendor setting, that is, using different MRI systems and acquisition protocols. In **Chapter 3**, a prospective pilot study is described assessing the reproducibility of cartilage T_2 measurements in four traveling volunteers over a 6-month-interval in a multicenter setting, using different MRI systems and sequence parameters. Volunteers were scanned on one day at five hospitals, and the same experiment was performed 6 months later. A good to excellent longitudinal reproducibility was found (ICCs ranging from 0.73 - 0.91 and RMS-CVs ranging from 1.1 - 1.5%). It should be noted that in this work, only healthy volunteers were studied. For future use of cartilage T_2 mapping as biomarker for (early) cartilage degeneration, it is essential to evaluate its responsiveness to change in patients suffering from OA and similar conditions.

2) Cross-validation of T_2 values in multicenter studies is important for assessing comparability of T_2 values across centers. As described in **Chapter 3** and in agreement with previous studies, T_2 values from different MRI scanners and from different vendors show considerable differences [30-32]. Several factors could have played a part in this issue, including coil type (in particular receive only versus receive and transmit coils) [33,34], magnetic field strength

[32,35,36], and T_2 mapping sequence variations (such as FSE versus SE and 3D versus 2D) [31,37,38]. T_2 mapping has considerable potential in musculoskeletal imaging, in particular given its feasibility in many types of scanners, yet the inter-scanner variation in T_2 values remains a matter of concern. Although beyond the scope of this thesis, future studies are needed to investigate the underlying causes of the differences in T_2 values across scanners and T_2 mapping sequences. Understanding these differences is critical for establishing common grounds and providing T_2 mapping protocols that generate comparable T_2 values across scanners. For now, it is important to realize that T_2 values obtained in different scanners should not be compared, nor pooled. In a study such as the *STARR trial*, one should focus on intra-subject change in T_2 values over time rather than absolute values of mean T_2 values across subject groups.

Feasibility of (q)MRI: reducing scan time

MRI allows evaluation of the whole knee, making it ideally suited to diagnose and monitor a broad range of musculoskeletal disorders [1,27]. MRI examination of the knee is, however, time consuming, especially when adding quantitative sequences such as T_2 mapping. Standard MRI knee protocol, including routine clinical sequences as well as T_2 mapping, typically takes about 30-45 minutes [12,39]. MRI examinations of the knee constitute a significant financial burden for societies; therefore, developing more streamlined protocols and accelerating image acquisition is therefore highly relevant [39]. Reducing scan time can not only save costs, it can also increase efficiency and patient comfort of MRI examinations [40].

In **Chapter 4**, we evaluated a promising new MRI technique to reduce scan time: the recently developed quantitative double-echo steady-state (qDESS) sequence. qDESS has the potential to provide diagnostic images and quantitative measurements of the knee in less than five minutes scan time [40,41]. Proof-of-concept of qDESS for T_2 mapping of cartilage and meniscus and structural knee imaging (using MOAKS) has been provided by Chaudhari et al. [40]. Focusing on healthy subjects, they validated qDESS against routine methods for T_2 mapping and MOAKS and reported high diagnostic performance for both cartilage and meniscus. Also, a pilot study in 10 patients with knee OA, performed in the same work, provided promising qDESS outcomes, suggesting that accurate knee OA measurements are possible with qDESS.

Building upon the work of Chaudhari et al., we further assessed the construct validity of quantitative and structural (semi-quantitative) qDESS-based biomarkers, in a larger OA cohort against radiography, widely accepted as the gold standard for OA knee imaging. We evaluated semi-quantitative MOAKS scores and T_2 measurements of the knee cartilage and meniscus in a clinical OA population (n = 53). The study population reflected a mix of different grades of OA severity: Kellgren-Lawrence Grade (KLG)0, KLG2 and KLG3 [42]. In contrast to the approach of Chaudhari et al., which encompassed global assessment of cartilage and meniscus, we evaluated predefined subregions. This is relevant as OA is a

focal disease; regions are not affected in the same rate and at the same time [43-47]. We demonstrated that T_2 mapping and structural (semi-quantitative) MRI knee assessment with MOAKS can distinguish between radiographic degree of OA, and that T_2 values were similar to the literature values [11,12,29,48]. The strongest correlations of qDESS with KLG was found in the medial femoral cartilage and medial posterior meniscal horn. These regional patterns were in line with previous work [3,49,50].

Our results highlight the potential value of qDESS for knee (OA) imaging and provide an important step in the further development and implementation of this technique. Further evaluation and validation of qDESS is needed, in particular, regarding the sensibility of qDESS to detect abnormalities in knee structures other than cartilage and meniscus, such as bone marrow lesions (BMLs, which can be a feature of OA or traumatic injury). In the literature, concerns have been raised that qDESS images underestimate the size of BMLs, possibly as a result of T_2* susceptibility effects [39,51]. Separation of the two qDESS echoes might improve accuracy for BML detection [40,52], yet further optimization is needed.

So far, qDESS studies have focused on knee OA; however, whether these results can be extended to *other patient groups*, is not clear. Thus, once qDESS is further optimized, it should be tested in musculoskeletal disorders other than OA. Another important limitation of qDESS studies so far is that only cross-sectional evaluation has been performed. The lack of a *longitudinal aspect* to these studies limits interpretation regarding its potential use in clinical trials.

Ultimately, one fast scan combining diagnostic image quality with qMRI, such as qDESS, may surpass traditional, time consuming MRI protocols. Deep learning-based methods for qDESS may further reduce scan time. This will allow more patients to be scanned within the existing workforce, thereby having tremendous implications for large-scale clinical studies and, potentially, clinical practice.

PART II: ETIOLOGY AND TREATMENT OF MENISCAL PATHOLOGY

The general aim of Part II of this thesis was to gain more insight into the role of meniscus damage in the development of knee OA, the classification "traumatic versus degenerative" tears, and into treatment strategies for meniscal pathology; they will be discussed in more detail in the next paragraphs.

The role of meniscus damage in knee OA: cause or consequence?

The fascinating role of the menisci in knee OA has increasingly gained attention from researchers worldwide. Not only can meniscal damage in an otherwise healthy knee lead to the development and progression of knee OA, knee OA might also lead to meniscal damage, which in turn can accelerate OA processes [53-61].

A generally accepted hypothesis is that due to morphological damage or extrusion, the meniscus may lose its critical biomechanical function load distribution and weight-bearing capacities within the knee joint are affected. Peak load may increase with 40 - 700% in the medial compartment [57], which may result in cartilage damage [54,62]. Cartilage loss may in turn cause further meniscal damage, creating a vicious circle of OA progression [54,55].

Exact pathophysiological processes in the development of knee OA and the complex interplay between different structures such as cartilage and menisci, however, remain largely unknown [63]. In particular, little consensus exists regarding the question of whether meniscal damage of cartilage damage comes first in the development of OA. According to some researchers, meniscal damage is the first sign of knee OA as MRI-confirmed meniscal damage often occurs prior to visible cartilage damage and as knees with meniscal damage, but without cartilage degradation, are at considerably higher risk of developing knee OA than knees with healthy menisci [43,53,57,64]. This view, however, is not generally accepted. Other researchers suggest that OA development starts with changes in cartilage, resulting in meniscal damage [65], or that meniscal damage and cartilage degradation occur in parallel as independent processes [66]. Due to difficulties in accurately monitoring the disease processes *in vivo* and the slow development of OA, studying such disease processes and spatial relationships is challenging [67].

To overcome this limitation, animal OA models are often used to gain knowledge of the pathophysiology and temporal sequence in OA development [66]. In an anterior cruciate ligament resected (ACLT) rabbit model for knee OA, meniscal damage has been found to occur prior to cartilage changes [68]. Contrary to what was suggested in the rabbit model, a study by Smith et al. using a dog ACLT model, has suggested that gross cartilage degradation occurs prior to gross meniscal damage [65].

In **Chapter 5**, we explored the relationship between cartilage and meniscus damage in the course of knee OA development in a collagenase-induced OA (CIOA) mouse model. Our study is the first to evaluate meniscal degeneration in the CIOA model. With this approach, OA is induced by an intra-articular injection of the enzyme collagenase [69,70]. Collagenase modifies the extracellular matrix of ligaments and other knee structures, inducing joint instability which subsequently causes knee OA. An advantage of this approach is, that the menisci are left untouched in inducing OA in the CIOA model, contrary to the surgical destabilization of the medial meniscus (DMM) mouse model (which is also frequently used as OA model) [71]. In our study, meniscal damage and cartilage damage appeared around the same time (2-4 weeks after OA induction). Furthermore, meniscal extrusion was observed early in the course of OA, from day 1 onwards.

These findings support the theory that meniscal extrusion, by altering load distribution within the knee joint, is an early sign of knee OA. Our findings must, however, be interpreted with caution as the findings of our mouse study might not apply in the same way to the

human knee. Also, it should be noted that the potential influence of the OA induction method (e.g. CIOA, DMM) on pathophysiological processes in OA and meniscal extrusion is not clear. Moreover, in general, meniscal extrusion is considered a radiographic (i.e., MRI-based) feature [62,72,73], but there is little evidence on histology-based meniscal extrusion.

It is clear that further research is required on the cascade in the development of knee OA and the temporal sequence of meniscal and cartilage damage during the course of OA. Understanding these processes is essential to developing and improving treatment strategies and, potentially, even prevention of knee OA. Future research should preferably be performed *in vivo*; after all, biomechanical and morphological features of the human knee differ from those of most animal knees [24,74]. In this context, qMRI techniques, such as T_2 mapping, may play an important role by allowing detection of very subtle changes in biochemical tissue composition in a non-invasive way [Chapter 2]. Especially T_2 mapping has high potential for this purpose as it does not require special MRI hardware [39]. Largescale longitudinal evaluation is needed to unravel disease pathways in the development of knee OA. The interplay between knee structures and the relation to *biomechanical*, *inflammation* and *clinical features* (e.g., knee pain) should be studied taking a comprehensive approach, involving all relevant knee structures and defined subregions.

The *continuum theory* of meniscal degeneration

In clinical decision making for meniscal pathology, in particular, in choice of treatment strategy, classifying meniscal tears as degenerative and traumatic tears plays a major role [55,75,76]. It must be recognized, however, that there is no consensus on how exactly to define "degenerative" versus "traumatic" tears. In fact, no strict morphological criteria exist to distinguish a degenerative from a traumatic meniscal tear; differentiation between those two types of tears can therefore be challenging. For instance, sometimes traumatic tears are a consequence of a very minor trauma (e.g., a misstep), and, on the other hand, degenerative tears can be present in what seems an otherwise ''healthy" knee" [77,78]. Also, meniscal tears are frequently observed incidental findings when performing knee MRI, without causing knee complaints [78]. Thus, differentiation between those two main types of tears is not as straightforward as it may seem.

Instead of the traditional classification of "degenerative" versus "traumatic" tears, one could think of a continuum from a healthy meniscus to a degenerative meniscus (Figure 1). In this theory, the chance of a "traumatic meniscal tear" depends on the degree of degeneration of the meniscal tissue: the more the degeneration, the higher the chance of a torn meniscus in the context of a traumatic event. This perspective would explain why sometimes a "traumatic meniscal tear" is seen following minor, low energy trauma [77]. A previous study has reported that traumatic meniscal tears may result from early degenerative disease processes, supporting the continuum hypothesis [79]. We performed a comprehensive, cross-sectional histology-based study, described in **Chapter 6**, using human meniscal tissue, to

test this hypothesis. Meniscal tissue from patients with traumatic meniscal tears (i.e., STARR trial participants) was compared to tissue from patients with acute transfemoral amputations with no history of knee injury (i.e., "healthy meniscal tissue"). Meniscal tissue from patients suffering from knee OA (i.e., "degenerative tissue") was used as reference standard. The study revealed that traumatically torn meniscal tissue showed a higher histological degree of degeneration compared to healthy meniscal tissue, thus, supporting the continuum theory.

Given the histology-based study design, longitudinal follow-up of meniscal tissue was not possible in our study; after all, meniscal tissue was histologically analyzed *after* resection. Although the potential influence of time-interval between injury and surgery was properly addressed (the statistical model was corrected for this factor), the lack of longitudinal assessment of tissue behavior should be acknowledged.

Thus, our results provide an important first step in testing the continuum theory of meniscal degeneration; however, findings need to be interpreted with care. Future research is required to understand how the biochemical composition of menisci changes from healthy tissue to different stages of degeneration and tears in knee OA and knee symptoms. In this context, one should realize that not all degenerative meniscal tears are symptomatic; thus, other factors must play a role in the production of symptoms.

Also, further work is needed to assess whether the continuum is two sided. If two sided, it would mean that meniscal tissue degeneration is more or less reversible, whether or not region-dependent. This hypothesis is supported by the finding that meniscal tissue is able to replace proteoglycans in early stage OA [80] and by the relatively high healing rates after meniscal repair reported in the literature, especially for tears in the red zone [81,82]. A study by Rubman and colleagues [83] reported that even tears that extend into the white (i.e., avascular) zone have the potential to fully heal after meniscal repair, especially longitudinal tears (though healing rates are lower compared to tears limited to the red zone). Tears in the lateral meniscus seem to heal better than tears in the medial meniscus [84]. It should be noted, however, that little consensus exists regarding what exactly comprises "full healing" after repair (e.g., absence on tear in intra-meniscal region, or 90% full thickness apposition of the original tear occurred with less than 10% of the tear remaining). Moreover, healing on MRI, healing in a second-look arthroscopy, and clinical healing (i.e., absence of symptoms) should not be assumed to be the same and are not necessarily correlated [83,85,86]. Further research on the continuum theory and what exactly happens on the molecular level is greatly needed, along with research on how those tissue changes are displayed in imaging parameters. In this context, great potential lies in the *in vivo* application of qMRI techniques such as T_2 mapping; to gain a deeper understanding of tissue behavior and further characterization of zonal differences. Ultimately, such knowledge may also contribute to clinical decision making for meniscal repair (e.g., to predict the chance of successful healing after repair based on tissue quality) and to the accurate assessment of healing response after repair.

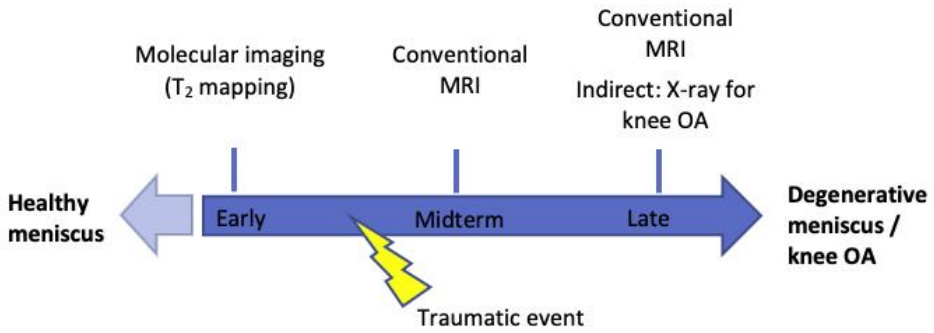


Figure 1. Schematic overview of the continuum theory of meniscal degeneration. During the course of the process from healthy meniscal tissue to meniscal degeneration (dark-blue arrow), optimal imaging techniques vary. Knee symptoms may occur in early phase, mid-term, late phase, or not at all. In this theory, a traumatic event (yellow thunderbolt-sign) can occur anywhere in the continuum and may accelerate the process of degeneration. The continuum potentially has a two-sided nature (light-blue arrow).

Clinical decision making in meniscal pathology: conservative versus arthroscopic treatment

"If it is torn, take it out, take it all out. Even if you just think it's torn, take it out". This statement by Smillie et al. in 1967 reflects the common approach to manage meniscal tears half a decade ago; total meniscectomy [60,87,88]. Since then, biomechanical studies and surgical outcome assessments, in particular regarding the substantially increased risk of knee OA after total meniscectomy, have increased our understanding of meniscal function and pathology [89-93]. Around the 1970's, when arthroscopic techniques were first introduced, a shift took place from total meniscectomy to removing only the damaged (i.e., torn) part of the meniscus (i.e., APM) [90-95]. For a long time, arthroscopic partial meniscectomy (APM) has been considered standard care for both degenerative and traumatic tears; a view based on the premise that APM often results in pain relief rather than evidence-based considerations [21,95-97]. APM is currently still the most performed orthopedic procedure in The Netherlands and in many other countries; indeed, each year over 40.000 of them are performed in our country [98-100]. However, a shift is taking place to a more evidence-based approach, which, in recent years, has led to a significant change in the treatment of meniscal tears [53,96,101,102].

Of key importance in this paradigm shift are several high-quality randomized controlled trials (RCTs) and meta-analyses that have been published recently comparing APM with non-operative therapy for patients with degenerative meniscal tears [103-107]. Most of these have reported no significant difference in clinical outcome between the two treatment strategies. These findings, and growing concerns regarding the increased risk of developing OA after APM [96,108,109], have led to much discussion on the treatment of degenerative meniscal tears. Non-operative therapy for meniscal tears is increasingly considered a serious treatment option rather than "masterly neglect" or "leaving the meniscal tear alone" [110-112].

A general consensus on the treatment of degenerative meniscal tears was reached in 2016 by the European Society of Sports Traumatology, Knee Surgery and Arthroscopy (ESSKA), providing a management algorithm which recommends starting with non-operative treatment (comprising exercise therapy and pain medication) [113].

For many years, studies comparing operative and non-operative treatment were limited to degenerative meniscal tears. Consequently, very little evidence is currently available for the efficacy of APM for traumatic tears. To address this gap in knowledge, we designed the STARR trial, an RCT comparing APM to non-operative treatment (i.e., exercise therapy and pain medication) in patients under 45 years old with traumatic meniscal tears (described in **Chapter 7).** Other institutions, such as the University of Southern Denmark, followed by starting comparable trials [114]. The relevance of such trials is obvious, but one should realize that conducting them is challenging. It often takes considerably more time than expected and scheduled, because of multiple factors.

As in many RCTs, a major issue in the STARR trial is the *availability of eligible patients.* To optimize methodological power, strict eligibility criteria are applied in the STARR trial. For instance, only patients with a solitary meniscal tear and no additional MRI findings in the knee (e.g., no cartilage lesions, anterior cruciate ligament ruptures) are included. A priori estimation of incidence of that specific injury was overstated and did not match reality; resulting in a considerable slower inclusion rate than scheduled. It is critical that, in future studies, more effort is taken to optimize the balance between scientific and pragmatic considerations, with the aim of high-quality yet feasible trials. In particular, an *a priori* defined realistic time frame, based on feasible inclusion rates, is highly relevant.

Another important issue concerning the slow inclusion rate in the STARR trial is the *current paradigm of traumatic meniscal tear treatment*, both for patients and orthopedic surgeons. In general, an overall consensus among clinicians has emerged that arthroscopic treatment is often not required for *degenerative* meniscal tears (although there remains a gap between scientific evidence and daily clinical practice). For treating *traumatic* meniscal tears, however, arthroscopy is still considered standard care by many orthopedic surgeons and by many patients. In general, this view has hampered their incentive to recruit patients for the STARR trial (as in the STARR trial, patients are randomized for either APM or non-operative treatment). In particular, the presence of locking complaints in the knee is often considered a valid indication for APM (although exactly what "locking complaints" entail is up for debate as no strict definition exists). Studies suggest, however, that locking complaints do not necessarily require arthroscopic treatment [115,116]. In fact, only a "fixed locked knee" (i.e., when a patient is completely unable to move the knee, generally caused by a dislocated meniscal tear) is a definite indication for arthroscopy [117]. Despite attempts to inform and instruct surgeons and patients carefully regarding the importance of scientific evidence, this treatment paradigm for traumatic meniscal tears seems, understandably, rather persistent. The online available

information for patients regarding the treatment of meniscal tears might also be contributing to this issue. For instance, the official website of the Dutch Association for Sports Medicine, as well as several websites of private clinics, indicates that arthroscopic treatment is required in the case of a meniscal tear [118-120]. This emphasizes the need for high-quality evidence regarding the treatment of traumatic meniscal tears.

Taking the current treatment paradigm into account, great care must be taken in implementing future results of studies such as the STARR trial in clinical practice, at the patient, the clinician, and the society level.

Clinical decision making in meniscal pathology: evidence-based patient selection for APM

A great deal of variability is seen in clinical factors that orthopedic surgeons use regarding the decision to perform APM; however, indication is not always evidence-based [101]. In this context, knowledge of prognostic factors for clinical outcome of APM on short-term and long-term could contribute to a more evidence-based patient selection for APM.

Various predictive factors for a worse clinical outcome of APM have been described in the literature, such as high BMI, meniscal extrusion and total meniscectomy [121,122]. The literature review in **Chapter 8** of this thesis was the first systematic review looking at prognostic factors for the clinical outcome after APM. We analyzed all available research describing clinical outcome after APM in mid-term and long-term (at least one-year follow-up). Based on the best available evidence, we concluded that the presence of radiographic knee OA, longer duration of complaints and resection of more tissue are associated with worse clinical outcome.

As a degenerative meniscal tear is associated with knee OA, one might expect that the classification of "degenerative versus traumatic" tears would have predictive value as well, that is, that degenerative tears would result in worse clinical outcome after APM. Surprisingly, this does not seem to be the case based on our systematic review. A possible explanation for this lies in the absence of a clear and widely accepted definition of "degenerative tear", as mentioned earlier. Also, the fact that a great deal of heterogeneity in the definition of subgroups and in outcome measures was observed across included studies might have played a role in this.

Our study results may contribute to the development of a prediction model for clinical outcomes of APM based on patient-dependent features. Such a model may be helpful in clinical decision making for meniscal pathology, potentially allowing a more evidence-based approach to patient selection for APM. In particular, the prognostic factor "presence of knee OA" is an interesting finding, especially with the potential of qMRI techniques, such as T_2 mapping, to detect subtle tissue changes and early stages of degeneration [Chapter 2].

It should be noted that, in this systematic review, only clinical outcome after APM was assessed. Although beyond the scope of our study, knowledge regarding the long-term radiological outcome of APM, in particular regarding the increased risk of developing OA, is clinically relevant as well. In addition, we did not include studies regarding meniscal repair but only studied prognostic factors for the outcome after APM, that is, meniscal resection. The rationale behind this approach was based on the clinical relevance of APM; the great majority of arthroscopies for meniscal tears comprise APM rather than repair.

Key points for future research

- *T_2 mapping of the meniscus* is a relatively new, yet highly potential technique. Proof-of-concept of T_2 mapping to assess meniscal degeneration using a standard fast spin echo sequence was provided in this thesis [Chapter 2] and previous studies [11,12]. In order to find its way in future implementation in clinical practice, the next step would be to confirm these findings in larger samples as well as in other patient groups (e.g., traumatic meniscal tears). In this context, we envision histology-based validation of *in vivo* meniscal T_2 mapping, including the assessment of meniscal zones.

- *Cartilage T_2 mapping* is shown to be capable of distinguishing degrees of OA (i.e., discriminative validity) and of providing longitudinal reproducibility. Hence, it has great potential as a non-invasive biomarker for tissue degeneration and is already used for longitudinal evaluation of cartilage degeneration in large clinical trials, such as the Osteoarthritis Initiative (OAI) [39,123]. The findings regarding inter-scanner variability in T_2 values in this thesis [Chapter 3] and previous work [30-32], however, remain a matter of concern. In the context of future studies comprising T_2 mapping in multicenter setting and, eventually, its implementation in clinical practice, future work on this issue is essential. Researchers should work together to further unravel underlying mechanisms causing the inter-scanner differences, using large-scale T_2 mapping data derived from various MRI systems and acquisition protocols. The ultimate goal would be a general consensus regarding standardized T_2 mapping protocols for each scanner type. Generating comparable T_2 values across different scanner and coil types might not be realistic goal, yet standardized algorithms for conversion factors across scanners might be valuable.

- *The 5-minute qDESS knee-MRI*, studied in this thesis, provides diagnostic image quality along with quantitative T_2 measurements of cartilage and meniscus in a single scan. Proof-of-concept [40] as well as construct validation in a clinical OA population [Chapter 4] shows the great potential of qDESS and provide a framework for further research. An important challenge lies in further optimizing qDESS in a way that all relevant knee structures and abnormalities can be assessed accurately, especially regarding bone marrow lesions. Subsequently, future studies evaluating the reliability of qDESS outcome parameters in terms

of longitudinal reproducibility (i.e., reliability of measuring intra-subject T_2 changes over time) are required. In the context of future implementation in clinical practice, further work is needed on the diagnostic performance of qDESS images for knee assessment.

- Further work is needed regarding *pathophysiological processes* in meniscal degeneration and the development and progression of knee OA. Key to all this is the interplay between relevant knee structures, such as the menisci and articular cartilage. Future studies should comprise multidimensional longitudinal analyses, focusing on spatial relationships between different knee structures and regions, and the association with biomechanical, inflammation, and clinical features. The approach we propose includes further investigating the causal chain of events in meniscal degeneration and the *continuum theory*. qMRI techniques such as T_2 mapping will be highly valuable in this context.

- Regarding clinical decision making for meniscal pathology, it has become increasingly clear that the treatment goal in patients with meniscal pathology does not only comprises rapidly restoring knee function and relieving pain, but also satisfactory long-term clinical outcomes and preservation of joint health [75,113]. This *shift in paradigm* towards a more evidence-based approach in clinical decision making will be enhanced by future study results of the STARR trial and comparable studies. Future cross-over analyses and knowledge of prognostic factors for the outcome of APM may provide valuable information regarding subsets of patients who are likely to benefit from APM. Non-invasive assessment of tissue quality, for instance using T_2 mapping, may in future help in clinical decision making. Also, T_2 mapping may potentially be a valuable tool to assess the reparability of meniscal tears on MRI and to evaluate outcomes of repair.

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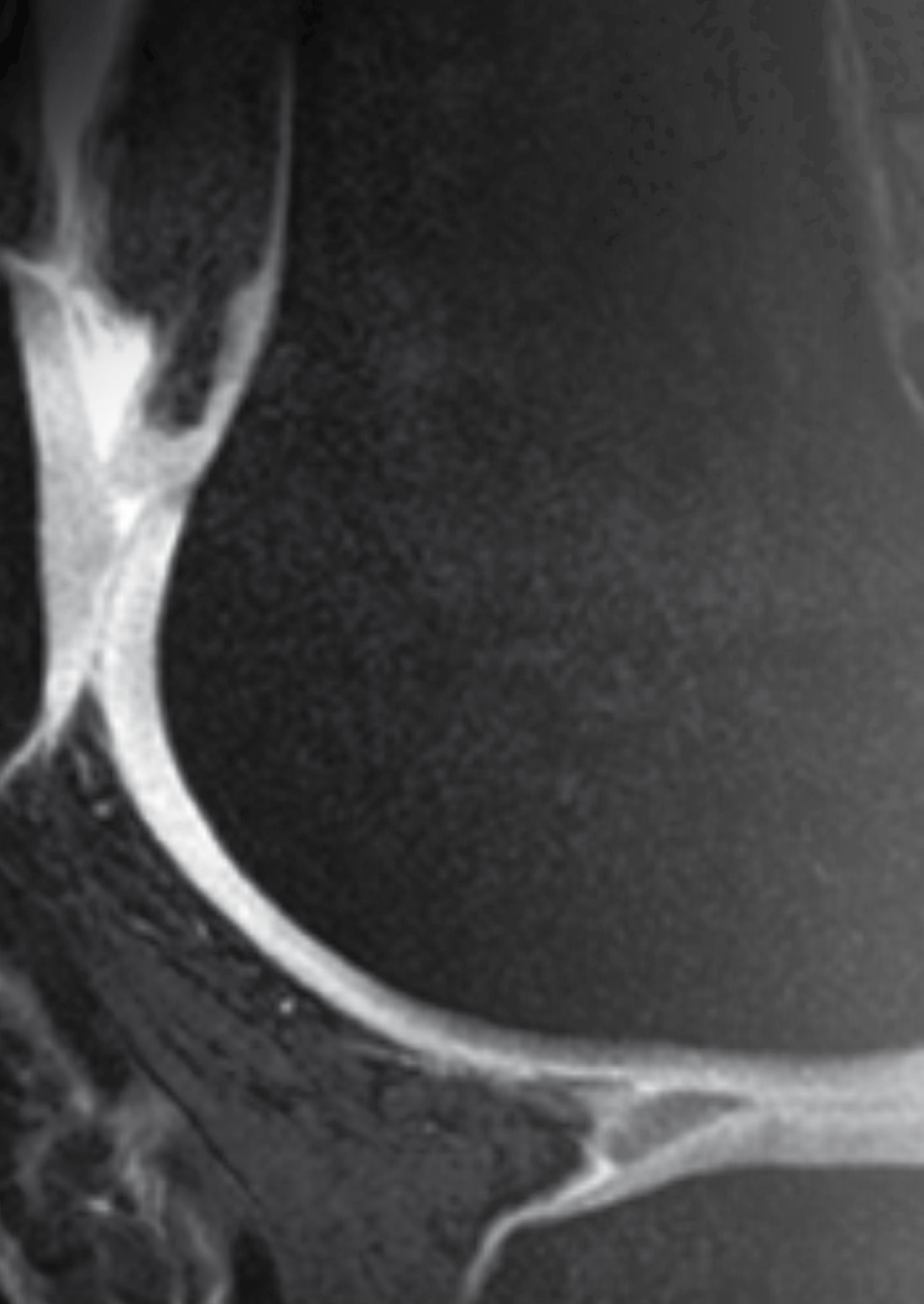

APPENDICES

Summary

The major biomechanical role of the meniscus within the knee joint and the relevance of meniscal integrity for the long-term health of the knee is becoming increasingly evident. In this thesis, several aspects of the meniscus are studied, comprising both basic science and clinical studies. The thesis is subdived into *two main themes*:

I) **Magnetic Resonance (MR) Imaging** of the meniscus (and cartilage), with the focus on quantitative MRI (qMRI) techniques. The validity and reproducibility of T_2 mapping, the most widely used qMRI technique in musculoskeletal research, are evaluated. Also, methods to increase efficiency in MRI acquisition of the knee, in particular regarding scan time, are investigated.

II) **Etiology and treatment** of meniscal pathology, with the aims to unravel etiologic processes and improve clinical decision making in meniscal pathology.

PART I: MR IMAGING OF MENISCAL PATHOLOGY

Validity and reproducibility of T_2 mapping as imaging biomarker in musculoskeletal research

In **Chapter 2**, a validation study of meniscal T_2 mapping is described. We prospectively validated *in vivo* T_2 mapping in menisci from OA patients against histological degree of degeneration. In this study, 13 menisci from seven patients were collected during total knee replacement surgery (Figure 1) and processed for histological analysis in a standardized way. Measurements were performed in the anterior and posterior meniscal horns. MRI examination of the knee was acquired on a 3-T scanner, one day prior to surgery. T_2 mapping analysis was performed using standard fast spin echo sequence with echo time values ranging from 3-27 ms. The histological degree of degeneration was measured using a validated scorings system, comprising the subdomains surface integrity, cellularity, collagen structure, and matrix staining (Figure 2). A strong correlation (r = 0.84, CI-95% 0.64-0.93) was found between T_2 measurements and the histological degree of degeneration. Although the study's sample size was relatively small, and it is not clear whether the results can be extended to pathologies other than knee OA, these findings suggest that fast spin echo based T_2 mapping can provide accurate T_2 measurements in menisci.

In **Chapter 3**, *reproducibility and multicenter comparability of cartilage T_2 mapping* was assessed. In the STARR trial, a clinical randomized controlled trial comparing operative and non-operative treatments for traumatic meniscal tears, T_2 mapping is used as outcome

measure for early cartilage degeneration. The STARR trial is a multicenter study with eight participating hospitals using various MRI systems and T_2 mapping sequences. To interpret cartilage T_2 data of STARR patients, information regarding reproducibility and comparability of T_2 values, acquired in different hospitals, will be essential. In this context, we performed a prospective pilot study in which cartilage T_2 mapping of four traveling healthy volunteers and a phantom was acquired at five different hospitals in one day. Each of the five hospitals is a participating center in the STARR trial, using various MRI systems (from different vendors) and T_2 mapping sequences.

To assess *longitudinal reproducibility* of T_2 measurements, the exact same experiment was performed six months later, using the same healthy volunteers. Six different cartilage regions of interest (ROIs) were included for each subject. Overall, the results showed a good to excellent longitudinal reproducibility of cartilage T_2 measurements over the six-months-interval, with ICCs ranging from 0.73 – 0.91 and RMS-CV values ranging from 1.1 – 1.5% for each ROI. Highest reproducibility was observed in the medial femoral cartilage, while lowest reproducibility was observed in the lateral tibial cartilage. RMS-CV values for longitudinal reproducibility of T_2 measurements for each hospital ranged from 0.6 – 1.6%. Due to the low sample size, ICCs for each center/hospital could not be reliably calculated. Lowest RMS-CVs (indicating highest reproducibility) were observed in Philips 3-Tesla and GE 3-Tesla scanners.

Cross-validation of T_2 measurements in this multicenter pilot study (**Chapter 3**) revealed significant differences in T_2 values across hospitals, both *in vivo* and in the phantom, similar to previous multicenter studies on T_2 mapping. Though outside the scope of the present thesis, underlying mechanisms in the T_2 differences across centers need to be unraveled. For now, we conclude that cartilage T_2 values from different hospitals should not be assumed to be comparable and should not be pooled.

Feasibility of (q)MRI: reducing scan time

Routine MRI examination of the knee, especially when adding quantitative imaging, generally takes up to 30-45 minutes. By providing quantitative measures of cartilage and meniscus and diagnostic image quality in a single MRI scan with an acquisition time less than five minutes, the recently developed quantitative double-echo steady-state (qDESS) MRI sequence for the knee has the potential to drastically reduce scan time. A single, rapid scan such as qDESS holds great promise, in particular, for longitudinal and large-scale clinical studies.

In **Chapter 4**, a validation study on qDESS is reported. Building upon a recently published proof-of-concept study of qDESS, we validated this new and promising technique in a clinical knee OA population (Figure 3). qDESS-based T_2 mapping of cartilage and menisci and structural (semi-quantitative) knee assessment in 53 subjects with different degrees of knee OA were found to be statistically significantly correlated with radiographic knee OA. Mean cartilage T_2 values were 36 ms in subjects without OA, 41 ms in those with mild OA, and 47

ms in those with moderate OA. Mean meniscal T_2 values were 15 ms in subjects without OA, 18 ms in those with mild OA, and 21 ms in those with moderate OA. T_2 measurements were found to be comparable with T_2 values in the literature. Although further research to optimize and validate qDESS is greatly needed, our findings show the potential value of qDESS.

PART II: ETIOLOGY AND TREATMENT OF MENISCAL PATHOLOGY

Etiology of meniscal pathology

In **Chapter 5**, the role of the meniscus in the development of knee OA, in particular the interplay between cartilage and meniscus degeneration, was studied in a mouse OA model. Histological degree of degeneration of menisci and cartilage was assessed at different time points during the course of OA (1, 3, 7, 14, 28 and 56 days after OA was induced). Also, meniscal extrusion (i.e., radial displacement of the meniscus) was evaluated at each time point. We found that cartilage and meniscus degeneration appeared around the same time (14 – 28 days after OA was induced) and that they were moderately correlated with each other. Moreover, meniscal extrusion was seen from day 1 onwards, suggesting that meniscal extrusion may represent early OA.

In **Chapter 6**, the etiology of meniscal pathology was investigated taking a clinical approach. We challenged the traditional classification of "traumatic" versus "degenerative" meniscal tears. We tested the theory that, instead of a clear-cut classification of traumatic and degenerative tears, a *continuum of degeneration* exists. Our hypothesis was that traumatically torn meniscal tissue shows more degeneration than intact tissue. A secondary aim was to identify patient specific factors that are associated with a higher degree of degeneration. In this histology-based study, meniscal tissue from patients with traumatic meniscal tears (obtained during arthroscopy, Figure 4) was compared to intact menisci (obtained during traumatic trans-femoral amputation or post-mortem). Meniscal tissue from patients with knee OA, obtained during total knee replacement surgery, was used as reference standard for degenerative menisci. After adjustment for sex, age, BMI, and time interval between trauma and surgery, patients with a traumatic meniscal tear showed a statistically significantly higher histological degree of degeneration than patients with intact meniscal tissue. No statistically significant difference in histological score was found between the traumatic and osteoarthritic group. In the traumatic group, no association between the degree of degeneration and time interval between trauma and surgery was observed. Moreover, no association was observed between degree of degeneration and the factors "age" and "sex". A statistically significant positive correlation between the patient specific factor "BMI" and histological degree of degeneration was found. Our findings support the continuum theory; however, further research is required on the etiology of meniscal pathology and the exact pathways from healthy meniscal tissue to degenerated meniscal tissue.

Clinical decision making in meniscal pathology

Although arthroscopic partial meniscectomy (APM) is the most performed orthopedic procedure in most western countries, no evidence is available comparing APM with non-operative treatment for traumatic meniscal tears. Therefore, we have designed and conducted the STARR trial, a multicenter randomized controlled trial (RCT), in which APM and non-operative (i.e., exercise) therapy are compared in patients aged 45 years or younger with traumatic meniscal tears. In **Chapter 7**, the design of the STARR trial is described. In total, 100 patients are included in the trial. After randomization, STARR patients are followed for two years, to investigate the differences between APM and exercise therapy in 1) clinical outcome (pain and function of the knee), 2) early signs of cartilage and meniscus degeneration on qMRI, and 3) cost-effectiveness of the treatments. The STARR trial is still ongoing, the results will be available at the end of 2020.

To increase evidence-based clinical decision making for meniscal tears, knowledge of prognostic factors for treatment outcomes is essential. In **Chapter 8**, a systematic review is presented on prognostic factors for the clinical outcome after APM. The study design of this review was in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) recommendations {Moher 2009}. Together with the biomedical literature specialist of our medical library, we systematically searched Medline, Embase, Cochrane, Web of Science, SPORTDiscus, Pubmed Publisher and Google Scholar databases, and article references. Articles reporting an association between patient-related or intra-articular factors and clinical outcome of APM, using validated questionnaires and with minimum follow-up of one year were included. Screening and quality assessment of selected studies was performed by two researchers independently. Out of 5150 potential eligible articles, identified by the search, 32 studies were included in this systematic review, comprising in total 4250 patients with a follow-up ranging from 1 to 13 years. Pooling the data was not appropriate due to considerable heterogeneity in the study population, subgroup definition, and outcome measures across included studies. Instead, a Best Evidence Synthesis was performed, by summarizing findings of included studies while taking the weight of the evidence into account. Moderate evidence was found showing that longer duration of symptoms (longer than one year), the presence of radiographic knee OA at baseline, and resecting more meniscal tissue during APM, are predictors for worse clinical outcome. Moreover, moderate evidence suggested that sex, pre-operative sport level, onset (i.e., traumatic versus degenerative), and type of meniscal tear are not prognostic factors for the clinical outcome after APM.

Chapter 9 comprises a general discussion encompassing the study results in this thesis. Moreover, clinical implications and future research perspectives are provided.

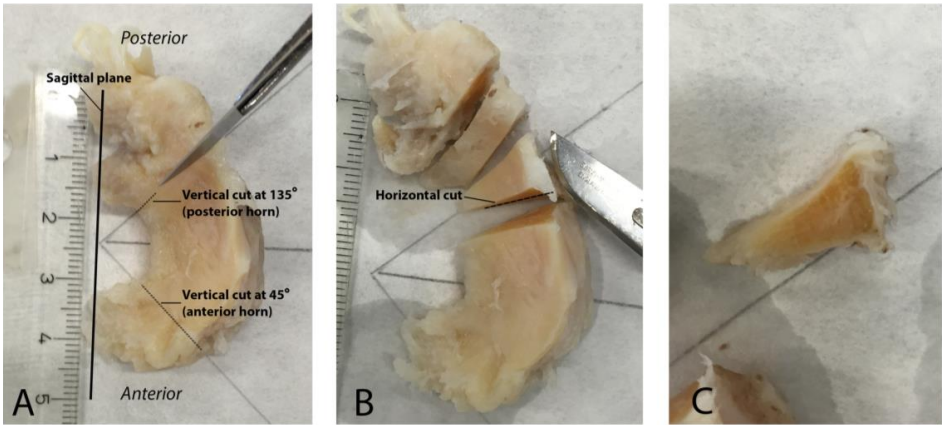

Figure 1. Preparation of meniscal samples. Example of a lateral meniscus harvested during total knee arthroplasty in a left knee of a 59-year-old female with medial compartment knee OA. A) Vertical cut. B) Horizontal cut. C) Detail view of vertical cut of the posterior horn.

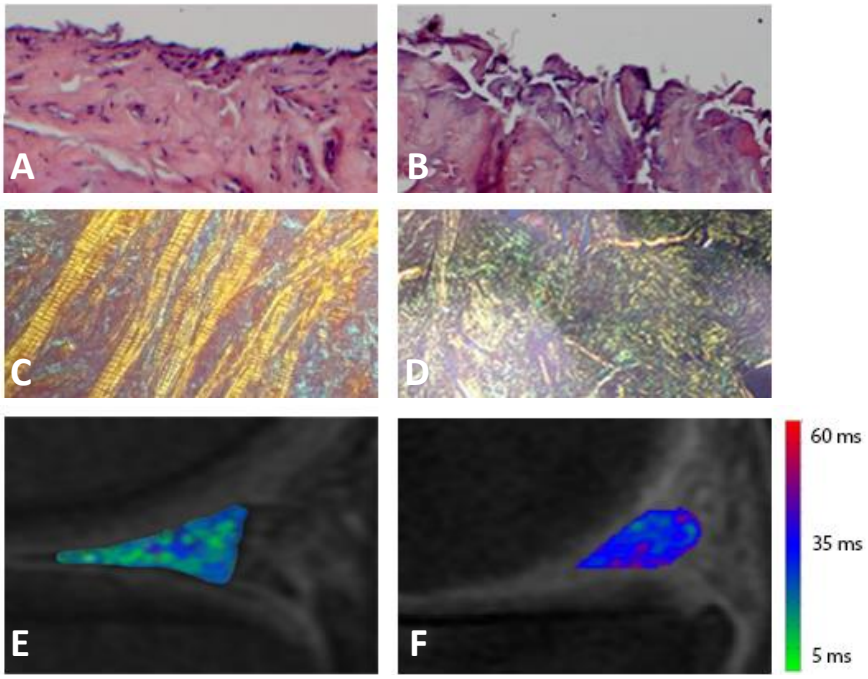

Figure 2. Histological findings in meniscal tissue and T_2 mapping images. A, C, E) Posterior horn of lateral meniscus of 67-year-old female with mild OA. B, D, F) Posterior horn of medial meniscus of 66-year-old female with severe OA. A, B) Surface integrity. C, D) Collagen organization. I, J) Corresponding T_2 mapping images with meniscal color maps.

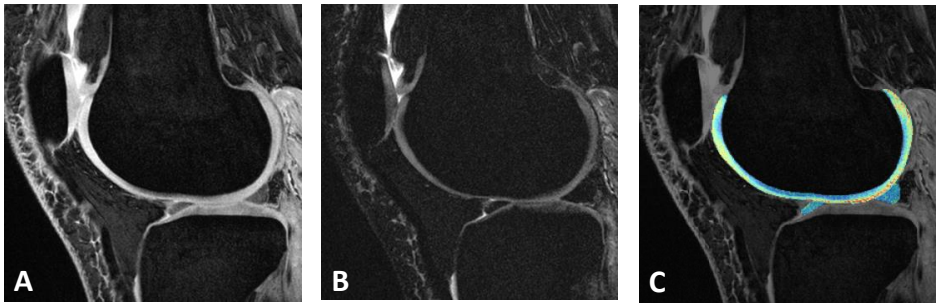

Figure 3. Representative example of sagittal qDESS images in 37-year-old female without OA, lateral knee compartment. A) First qDESS echo, TE 5.7 ms. B) Second qDESS echo, TE 30.1 ms. C) Corresponding T_2 color maps of cartilage and meniscus.

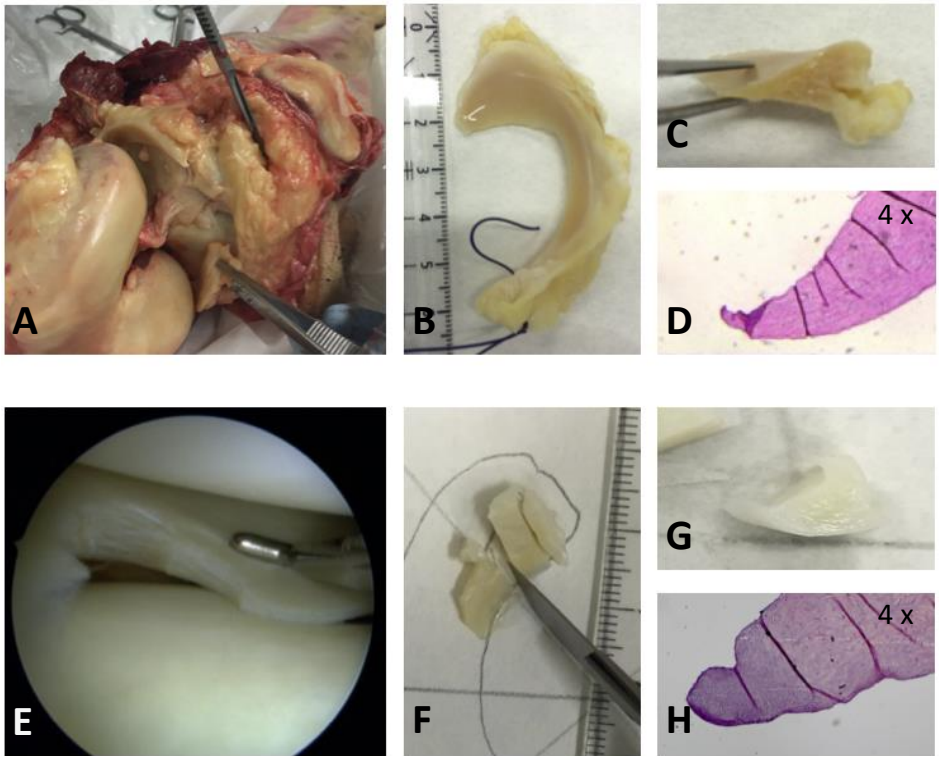

Figure 4. Harvesting and processing meniscal tissue. A) Harvesting of intact menisci in 53-year-old male during transfemoral amputation. B) Macroscopic view of medial meniscus after harvesting. C) Vertical cut of medial posterior horn. D) Corresponding histological section (HE staining). E) Harvesting of traumatically torn meniscal tissue in 39-year-old male during arthroscopic partial meniscectomy. F) Meniscal tissue after harvesting (medial meniscus). G) Vertical cut. H) Corresponding histological section (HE staining).

Nederlandse samenvatting

Er wordt steeds meer duidelijk over de belangrijke biomechanische rol van de meniscus binnen het kniegewricht en het belang van een goed werkende meniscus voor een gezonde knie functie op de lange termijn. In dit proefschrift komen verschillende aspecten van de meniscus aan bod, zowel binnen de basale wetenschap als binnen het klinisch onderzoek. Het proefschrift is onderverdeeld in twee hoofd thema's:

I) **Magnetic Resonance (MR) Imaging** van de meniscus (en kraakbeen), met de focus op kwantitatieve MRI (qMRI) technieken. De validiteit en reproduceerbaarheid van T_2 mapping, de meest gebruikte qMRI techniek in musculoskeletaal onderzoek, zijn geëvalueerd. Ook zijn er methoden onderzocht om de efficientië van MRI acquisitie van de knie te verhogen, met name gericht op het reduceren van scantijd.

II) **Etiologie en behandeling** van meniscus pathologie, met het doel om meer duidelijkheid te verkrijgen over etiologische processen en het verbeteren van ''clinical decision making" voor meniscus pathologie.

DEEL I: MR IMAGING VAN MENISCUS PATHOLOGIE

Validiteit en reproduceerbaarheid van T_2 mapping als imaging biomarker in musculoskeletaal onderzoek

In **Hoofdstuk 2** wordt een validatie studie naar meniscus T_2 mapping beschreven. We hebben *in vivo* T_2 mapping in menisci van artrose patiënten prospectief gevalideerd tegen histologische mate van degeneratie. In deze studie zijn 13 menisci van zeven patiënten verzameld tijdens totale knie vervangende chirurgie (Figuur 1 van Summary) en verwerkt voor histologische analyse op gestandardizeerde wijze. Metingen zijn verricht in de meniscus voor- en achterhoorn. MRI van de knie werd verricht op een 3-T scanner, een dag voor de operatie. T_2 mapping analyse werd verricht met een standaard fast spin echo sequence met echo tijden tussen de 3-27 ms. De histologische mate van degeneratie werd gemeten met een gevalideerd scorings systeem, bestaande uit de subdomeinen: oppervlakte integriteit, cellulariteit, collageen structuur, en matrix aankleuring (Figuur 2 van Summary). Een sterke correlatie (r = 0.84, CI-95% 0.64-0.93) werd gevonden tussen T_2 waarden en histologische mate van degeneratie. Hoewel de sample size van de studie relatief klein is en het niet zeker is of de resultaten geëxtrapoleerd kunnen worden naar andere aandoeningen dan knie artrose, suggereren deze resultaten dat met fast spin echo-based T_2 mapping accurate T_2 metingen in menisci verkregen kunnen worden als maat voor degeneratie.

In **Hoofdstuk 3** is er gekeken naar *reproduceerbaarheid en vergelijkbaarheid van T_2 mapping in kraakbeen*. In de STARR trial, een klinische gerandomiseerde trial waarbij operatieve en niet-operatieve behandeling van traumatische meniscusscheuren worden vergeleken, wordt T_2 mapping gebruikt als uitkomstmaat voor vroege kraakbeen- en meniscus schade. De STARR trial is een multicenter trial waarin acht ziekenhuizen participeren, met verschillende MRI systemin en T_2 mapping protocollen. Om de T_2 data van kraakbeen en menisci te kunnen intepreteren is kennis met betrekking tot reproduceerbaarheid en multicenter vergelijkbaarheid van T_2 waarden, afkomstig uit verschillende ziekenhuizen, essentieel. In dit kader hebben wij een prospectieve pilot studie uitgevoerd waarbij kraakbeen T_2 waarden van vier gezonde vrijwilligers en een fantoom, gescand in vijf verschillende ziekenhuizen (allemaal op dezelfde dag), werden vergeleken. Het ging hierbij om STARR-gelieerde centra met verschillende MRI systemen.

Om de *reproduceerbaarheid van* T_2 metingen over de tijd te beoordelen, werd een identiek experiment zes maanden na de baseline metingen uitgevoerd, met dezelfde gezonde vrijwilligers. Zes verschillende kraakbeen regio's werden geïncludeerd per knie. Over het algemeen laten de resultaten een goede tot uitstekende reproduceerbaarheid van T_2 metingen zien over het zes-maanden-interval, met ICCs varierend van 0.73 – 0.91 en RMS-CV waarden van 1.1 – 1.5%. De hoogste reproduceerbaarheid werd gezien in het mediale femur kraakbeen, het laterale tibia kraakbeen scoorde het laagst. RMS-CV waarden voor de reproduceerbaarheid van T_2 metingen over de tijd voor elk ziekenhuis apart varieerden van 0.6 – 1.6%. De laagste RMS-CV waarde en dus de hoogste reproduceerbaarheid werd gevonden in Philips 3-Tesla en GE 3-Tesla scanners. Door de lage aantallen (n = 4) was het niet mogelijk om op betrouwbare wijze ICCs voor elk ziekenhuis apart te berekenen.

Cross-validatie van T_2 metingen in de betreffende multicenter pilot studie (**Hoofdstuk 3**) liet significante verschillen in T_2 waarden tussen ziekenhuizen zien, zowel *in vivo* als in het fantoom, vergelijkbaar met eerdere multicenter studies over kraakbeen T_2 mapping. Hoewel buiten de scoop van het huidige onderzoek, is het van belang de onderliggende mechanismen achter de gevonden verschillen in T_2 waarden tussen ziekenhuizen te onderzoeken. Voor nu concluderen we dat kraakbeen T_2 waarden, verkregen uit verschillende ziekenhuizen, niet zonder meer vergeleken danwel gepooled mogen worden.

Reduceren van scantijd bij qMRI

Een MRI scan protocol voor de knie, inclusief kwantitatieve metingen, duurt momenteel ca. 30-45 minuten. De recent ontwikkelde quantitative double-echo steady-state (qDESS) MRI techniek voor de knie combineert diagnostische beeldkwaliteit met kwantitatieve metingen van kraakbeen en meniscus in een enkele MRI scan met acquisitie tijd van minder dan vijf minuten. qDESS heeft hierdoor de potentie om scantijd drastich te reduceren. Deze techniek is veelbelovend, In het bijzonder voor longitudinale en/of grootschalige klinische studies.

In **Hoofdstuk 4** wordt een validatie studie naar qDESS beschreven. Voortbordurend op een recent gepubliceerde qDESS proof-of-concept studie, hebben we deze innovatieve techniek gevalideerd in een klinische knie artrose populatie (Figuur 3 van Summary). Met qDESS verkregen T_2 mapping van kraakbeen en menisci en structurele (semi-kwantitatieve) knie scores in 53 patiënten met verschillende gradaties knie artrose waren statistisch significant gecorreleerd aan radiologische mate van artrose. Gemiddelde kraakbeen T_2 waarden waren 36 ms in personen zonder artrose, 41 ms in patiënten met milde artrose, en 47 ms in patiënten met matige artrose. De gemiddelde meniscus T_2 waarden bedroegen 15 ms in personen zonder artrose, 18 ms in patiënten met milde artrose, and 21 ms in patiënten met matige artrose. De gevonden T_2 waarden bleken redelijk overeen te komen met T_2 waarden uit de literatuur. Onze resultaten laten de potentiële waarde en toepasbaarheid van qDESS voor knie artrose zien; nadere optimalisatie van de techniek en validatie van qDESS in grotere groepen en andere pathologie is uiteraard noodzakelijk.

DEEL II: ETIOLOGIE EN BEHANDELING VAN MENISCUS PATHOLOGIE

Etiologie van meniscus pathologie

Hoofdstuk 5 beschrijft een studie naar de rol van de meniscus in het ontwikkelen van knie artrose, in het bijzonder de wisselwerking tussen kraakbeen en meniscus degeneratie, in een muis model. De histologische mate van degeneratie van menisci en kraakbeen werd beoordeeld op verschillende tijdpunten gedurende de ontwikkeling van knie artrose (1, 3, 7, 14, 28 en 56 dagen na artrose inductie). Ook werd de mate van meniscus extrusie (d.w.z. de zijwaartse verplaatsing van de meniscus) geëvalueerd op elk tijdpunt. Onze resultaten lieten zien dat kraakbeen en meniscus degeneratie rond dezelfde tijd ontstaat (14 – 28 dagen na artrose inductie) en dat deze matig gecorreleerd zijn aan elkaar. Meniscus extrusie werd gezien vanaf dag 1 na artrose inductie, suggererend dat meniscus extrusie mogelijk vroege artrose representeert.

In **Hoofdstuk 6** hebben we de etiologie (d.w.z. onstaanswijze) van meniscus pathologie onderzocht vanuit een klinisch perspectief, waarbij de traditionele classificatie van "traumatische" versus "degeneratieve" meniscus scheuren betwist werd. Onze hypothese was, dat in plaats van een dichotome classificatie tussen traumatische en degeneratieve scheuren, er een continuüm van degeneratie bestaat. In dit continuüm loopt de mate van degeneratie op in een cascade van gezond meniscus weefsel tot degeneratief weefsel, waarbij de kans op een meniscus scheur bij knietrauma toeneemt bij meer degeneratie. In ons onderzoek werd meniscus weefsel van patiënten met traumatische meniscus scheuren (verkregen tijdens arthroscopie, Figuur 4 van Summary) vergeleken met intacte gezonde menisci (verkregen tijdens traumatische bovenbeenamputaties of post mortem). Meniscus weefsel van knie

artrose patiënten (verkregen tijdens knie vervangende chirurgie) werd gebruikt als referentie meting voor degeneratief weefsel. Na correctie voor geslacht, leeftijd, BMI en tijdinterval tussen trauma en operatie, vertoonden patiënten met traumatische meniscus scheuren een statistisch significant hogere mate van degeneratie dan patiënten met intact meniscus weefsel. Geen statistisch significant verschil in mate van degeneratie werd gevonden tussen traumatisch gescheurd en degeneratief weefsel. In de groep met traumatisch gescheurd weefsel werd geen verband gevonden tussen het tijdinterval tussen trauma en operatie en mate van degeneratie. Ook werd er geen significant verband gezien tussen de mate van degeneratie en de factoren geslacht en leeftijd. Wel werd er een statistisch significante correlatie gevonden tussen het BMI van de patiënt en de mate van degeneratie. Onze bevindingen ondersteunen de continuüm theorie en bieden aanknopingspunten voor verder onderzoek. De pathofysiologische mechanismen die een rol spelen bij de cascade van gezond meniscus weefsel tot degeneratief weefsel, en het onderscheid tussen artrose- versus ouderdomsgerelateerde weefsel degeneratie zijn hierbij belangrijke invalshoeken.

"Clinical decision making" voor meniscus pathologie

Hoewel arthroscopische partiële meniscectomie (APM) de meest verrichte orthopedische ingreep is in westerse landen, is er geen wetenschappelijk bewijs beschikbaar voor de effectiviteit van APM ten opzichte van niet-operatieve behandeling van traumatische meniscus scheuren. Om dit kennishiaat op te vullen hebben we vanuit het Erasmus MC in 2014 de STARR trial geïnitieerd, een multicenter randomized controlled trial (RCT), waarin APM en niet-operatieve behandeling (fysiotherapie) worden vergeleken in patiënten onder de 45 jaar met traumatische meniscus scheuren. In **Hoofdstuk 7** wordt het studieprotocol van de STARR trial beschreven. In totaal zijn er 100 patiënten geïncludeerd in de trial. Na randomizatie worden STARR patiënten voor twee jaar gevolgd, om de verschillen tussen APM en fysiotherapie te onderzoeken met betrekking tot 1) klinische uitkomst (pijn en functie) 2) vroege tekenen van knie artrose op qMRI, en 3) kosten-effectiviteit van de behandelingen. De STARR trial is nog lopende, de resultaten zullen eind 2020 beschikaar zijn.

Om een meer 'evidence-based' clinical decision making voor meniscus letsel te faciliteren, is kennis van prognostische factoren voor therapie uitkomsten essentieel. **Hoofdstuk 8** beschrijft een systematisch literatuuronderzoek naar prognostische factoren voor de klinische uitkomst na APM. Het studie ontwerp van dit review was in overeenstemming met de Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) aanbevelingen. Samen met de biomedisch literatuur specialist van onze medische bibliotheek doorzochten we op systematische wijze de databases Medline, Embase, Cochrane, Web of Science, SPORTDiscus, Pubmed Publisher en Google Scholar databases, en artikel referenties. Artikelen die een associatie tussen patiënt-gerelateerde of intra-articulaire factoren en klinsche uitkomst van APM rapporteerde, waarbij gebruik werd gemaakt van gevalideerde vragenlijsten en met minimaal een jaar follow-up werden geïncludeerd. Screening en kwaliteitscontrole van

de geselecteerde studies werd verricht door twee onderzoekers, onafhankelijk van elkaar. Uit 5150 potentieel geschikte artikelen, geïdentificeerd door de database search, werden er 32 studies geïncludeerd in dit systematische review, in totaal 4250 patienten omvattend met een follow-up duur tussen de 1 en 13 jaar. Pooling van de data was niet mogelijk door aanzienlijke heterogenitieit in de studie populatie, in subgroep definities, en in uitkomst maten tussen geïncludeerde studies. Er werd daarom een ''Best Evidence Synthesis" verricht, waarbij bevindingen van geïncludeerde studies werden geanalyseerd gebruik makend van een weegfactor voor de bewijskracht van de studies. Er werd matig bewijs gevonden voor de voorspellende waarde van een langere duur van klachten (meer dan een jaar), voor de aanwezigheid van radiologische artrose ten tijde van de operatie en voor het peroperatief verwijderen van meer meniscus weefsel op een slechtere klinische uitkomst. Ook werd er matig bewijs gevonden dat geslacht, pre-operatief sport niveau, ontstaanswijze (traumatisch versus degeneratief), en type scheur geen prognostische factoren zijn voor de klinische uitkomst na APM.

Hoofdstuk 9 omvat een algemene discussie van de studieresultaten in dit proefschrift. Tevens worden er klinische implicaties en perspectieven voor toekomstig onderzoek beschreven.

List of abbreviations

ACL = Anterior cruciate ligament
ACR = American College of Rheumatology
ANOVA = Analysis of variance
APM = Arthroscopic partial meniscectomy
BMI = Body mass index
CIOA = Collagenase-induced osteoarthritis
CONSORT= Consolidated Standards of Reporting Trials
DMM = Destabilization of the medial meniscus
FSE = Fast spin echo
FSPGR = Fast-spoiled gradient-echo
ICC = Intraclass correlation coefficient
IKDC = International Knee Documentation Committee
ICRS = International Cartilage Repair Society
IQR = Inter quartile range
KLG = Kellgren and Lawrence grade
KOOS = Knee injury and Osteoarthritis Outcome Score
MOAKS = MRI osteoarthritis knee score
MR = Magnetic resonance
NRS = Numeric rating scale
OA = Osteoarthritis
PRISMA = Preferred Reporting Items for Systematic Review and Meta-analysis Protocols
Prospero = International Prospective Register for Systematic Reviews
qDESS = Quantitative double-echo steady-state
qMRI = Quantitative magnetic resonance imaging
RCT = Randomized controlled trial
RMS-CV = Root mean square of coefficient of variation
ROI = Region of interest
SD = Standard deviation
SE = Spin echo
SPIRIT = Standard protocol items: recommendation for interventional trials
SNR = Signal-to-noise ratio
TE = Echo time
3-T = 3 Tesla
95%-CI = 95% confidence interval

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''Alleen het dankwoord wordt gelezen"
- Joyce

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About the author

Susanne Martine Eijgenraam received her BSc in Biomedical Science in 2009 from Vrije Universiteit Amsterdam and was subsequently selected to obtain a master degree in Medicine and Clinical Research at Maastricht University Medical Center. For her master thesis, she developed and validated a digital software tool to determine vertebral rotation on X-rays, which resulted in her first publication, and planted the seed for a scientific career.

She finished her double master program in 2014, and returned to her hometown Rotterdam to start as a PhD-candidate at Erasmus MC, on imaging and treatment of meniscal pathology, a collaboration between the dept. of Orthopedic Surgery and the dept. of Radiology. Together with her supervisors, Susanne set up and coordinated the world's first multicenter RCT on clinical and radiological outcomes of surgical vs. non-surgical treatment for traumatic meniscal tears: the STARR trial. In addition, she initiated several research projects, mainly focusing on molecular imaging of the meniscus, eventually forming the base of this thesis.

In 2017 and 2018, she spent several months as visiting researcher at the Joint and Osteoarthritis Imaging with Novel Technology (JOINT) lab of Stanford University (USA), supervised by prof. Garry Gold, to work on a project on a 5-minute MRI scan of the knee, funded by two Junior Researcher grants. She has presented her work at many national and international conferences and was awarded for Best Oral presentation twice.

Besides research, Susanne has a special interest in education; she was a student member of the Educational Board of Medicine during her master program, and conducted several teaching activities during her PhD period.

During her time as PhD-candidate her passion for imaging was fueled; she chose a career in radiology and started residency at Erasmus MC in the spring of 2019. Susanne lives with her boyfriend Kees in Rotterdam. When not working she enjoys parties, yoga, guitar, reading, snowboarden and surfing.

PhD Portfolio

Personal Details	
Name	Susanne M. Eijgenraam
Department	Dept. of Radiology & Nuclear Medicine Dept. of Orthopedic Surgery
PhD period	2014 - 2019
Promotor	Prof. S.M.A. Bierma-Zeinstra
Co-promotoren	Dr. E.H.G. Oei Dr. M. Reijman Dr. D.E. Meuffels

Courses: General	**Year**	**ECTS***
Basiscursus Regelgeving en Organisatie van Klinische Trials / Good Clinical Practice (Erasmus MC)	2014	1
Website Development (Alterian, Erasmus MC)	2014	0.3
Endnote (Medical Library, Erasmus MC)	2014	0.2
Systematic literature search strategies (Medical Library, Erasmus MC) I + II	2014	0.5
Presentation and Pitch Training (Erasmus MC)	2015	0.5
Presentation Skills (Anne Gehring, Amsterdam)	2015	2
Research Integrity (Erasmus MC)	2015	0.3
Biomedical Writing and Communication (Erasmus MC)	2016	3
HIPPOS (Stanford University)	2017	0.3

Courses: Statistics (NIHES)	**Year**	**ECTS***
Introduction to Data Analysis	2014	2
Clinical Trials	2015	2
Meta-analyses	2015	2
Regression Analysis	2016	2
Repeated Measurements	2017	2

Courses: Teaching Skills	**Year**	**ECTS***
Course "Coaching Medical Students I" (Erasmus MC)	2016	0.2
Course "Teach the Teacher" (Basis didactiek) - BKO	2016	2
Course "Hoorcollege geven" - BKO	2017	0.2
Course "Omgaan met groepen" - BKO	2017	0.2
Course "Coaching Medical Students II" (Erasmus MC)	2017	0.2
Course "Examenvragen maken" - BKO	2018	0.2

Courses: Imaging	Year	ECTS*
MRI Safety and Scanning (Dept. of Radiology, Erasmus MC)	2014	2
Basic Course in Applied MRI Techniques (ESMRMB)	2016	1.5

(Inter)national Podium Presentations	Year	ECTS*
Development and assessment of a digital X-ray software tool to determine vertebral rotation in AIS *Nordic Spinal Deformities Society Annual Meeting, Amsterdam, The Netherlands*	2015	1
Cartilage T_2 Mapping Relaxation Times: Reproducibility in a Multicenter Trial *Nordic Cartilage Imaging Meeting, Utrecht, The Netherlands*	2015	1
Predictors for the Clinical Outcome of Arthroscopic Partial Meniscectomy - a Systematic Review *Nederlandse Vereniging voor Orthopedie (NOV) Fall Meeting, Veldhoven, The Netherlands*	2016	1
T_2 Mapping Correlates with Histopathological Degree of Meniscal Degeneration – An in-vivo validation study *Nederlandse Vereniging voor Arthroscopie (NVA) Annual Meeting, Rotterdam, The Netherlands* Award for best abstract and presentation	2017	1
T_2 Mapping Correlates with Histopathological Degree of Meniscal Degeneration – An in-vivo validation study *European Congress of Radiology (ECR), Vienna, Austria*	2017	1
T_2 Mapping Correlates with Histopathological Degree of Meniscal Degeneration – An in-vivo validation study *Radiologen Dagen, Rotterdam, The Netherlands*	2017	1
T_2 Mapping Correlates with Histopathological Degree of Meniscal Degeneration – An in-vivo validation study *ISAKOS World Congress, Shanghai, China (held by D. Meuffels)*	2017	0.3
Quantitative MRI techniques in knee Osteoarthritis – MyThesisIn3Minutes *European Congress of Radiology (ECR), Vienna, Austria* Award for best oral presentation in MSK	2018	1
Molecular imaging in musculoskeletal research - an overview *Int. Workshop of Molecular Imaging Erasmus MC, Rotterdam, The Netherlands*	2018	1
Simultaneous T_2 mapping and morphological imaging of the osteoarthritic knee using a rapid 5-minute DESS MRI scan *Int. Workshop of Osteoarthritis Imaging, Menton, France*	2018	1
Simultaneous T_2 mapping and morphological imaging of the osteoarthritic knee using a rapid 5-minute DESS MRI scan *European Congress of Radiology (ECR), Vienna, Austria* Nominated for best oral presentation in MSK	2019	1
Novel insights into imaging and treatment of traumatic meniscal tears *Nederlandse Vereniging voor Sportgeneeskunde (NVS) Annual Meeting, Ermelo, The Netherlands*	2019	1

(Inter)national Poster Presentations	Year	ECTS*
Predictors for the Clinical Outcome of Arthroscopic Partial Meniscectomy - a Systematic Review *OARSI World Meeting, Amsterdam, The Netherlands*	2016	0.5
Cartilage T_2 Mapping Relaxation Times: Reproducibility in a Multicenter Trial *Int. Workshop of Osteoarthritis Imaging, Oulu, Finland*	2016	0.5
Simultaneous T_2 mapping and morphological imaging of the osteoarthritic knee using a rapid 5-minute DESS MRI scan *ISMRM Annual Meeting, Paris, France*	2018	0.5

Teaching Activities and Student Supervision	Year	ECTS*
Teaching assistant microscopic bone pathology for first year medical students (annually)	2014-2018	1
Teaching Statistics to master- students (annually)	2014-2017	1
Teaching assistant minor "musculoskeletal system" (medical students)	2014-2017	1
Coaching medical bachelor students (6 students)	2015-2019	3
Supervising Master-student Frans Bovendeert – Correlation between Meniscal T_2 Mapping and Histopathological Degree of Degeneration	2016	4
Supervising Master-student Tim Wesdorp – Histological Degree of Degeneration of Traumatically Torn Meniscal Tissue	2017	4

Total Workload in ECTS*	**50.4**

Grants	Year
Conference Travel Grant *Erasmus Trustfonds*	2015
Young Researcher Grant 2017 *Osteoarthritis Research Society International (OARSI)*	2017
Young Researcher Grant 2017 *European Society of Musculoskeletal Radiology (ESSR)*	2017
Rising Star / Invest in the Youth Grant 2018 *European Society of Radiology (ESR)*	2018
Rising Star / Invest in the Youth Grant 2019 *European Society of Radiology (ESR)*	2019

Awards	Year
Eikelaar Award for Best Abstract and Presentation *NVA Annual Meeting*	2017
Award for Best Oral Presentation *My Thesis in 3 Minutes, European Congress of Radiology (ECR)*	2018

Organizing activities	Year
Co-organizing Ski-weekend *Dept. of Orthopedic Surgery, Erasmus MC*	2015
Co-organizing Refereeravond "Cartilage Imaging" *Dept. of Radiology, CZE, Eindhoven, The Netherlands*	2015
Co-organizing Orthopaedie-dag *Dept. of Orthopedic Surgery, Erasmus MC*	2016
Co-organizing International Workshop Molecular Imaging *Dept. of Radiology, Erasmus MC*	2018
Co-organizing International Workshop of Osteoarthritis Imaging *Dept. of Radiology, Erasmus MC*	2020

Other scientific activities	Year
Journal Reviewer for Journal of Advances in Radiology and Medical Imaging	2016-now
Journal Reviewer for Annuals of Rheumatic Diseases	2016-now
Journal Reviewer for European Journal of Radiology	2016-now
Journal Reviewer for Seminars in Arthritis and Rheumatism	2019-now
Visiting researcher at JOINT-lab (PI: Garry Gold, MD) for 3 months *Dept. of Radiology, Stanford University, Ca, U.S.A.*	2017
Visiting researcher at JOINT-lab (PI: Garry Gold, MD) for 2 months *Dept. of Radiology, Stanford University, Ca, U.S.A.*	2018

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

List of publications

SK Schmitz, JJ Hjorth, RM Joemai, R Wijntjes, **SM Eijgenraam**, P de Bruijn, C Georgiou, AP de Jong, A van Ooyen, M Verhage, LN Cornelisse, RF Toonen, WJ Veldkamp. Automated analysis of neuronal morphology, synapse number and synaptic recruitment. *J Neuros I Methods.* 2011;195(2):185-93

SM Eijgenraam, TF Boselie, JM Sieben, CH Bastiaenen, PC Willems, C Arts, A Lataster. Development and assessment of a digital X-ray software tool to determine vertebral rotation in adolescent idiopathic scoliosis. *Spine J.* 2017;17:260-265

SM Eijgenraam, M Reijman, SMA Bierma-Zeinstra, DT van Yperen, DE Meuffels. Can we predict the clinical outcome of arthroscopic partial meniscectomy? A systematic review. *Br J Sports Med.* 2018;52(8):514-521

AS Chaudhari, MS Black, **SM Eijgenraam,** W Wirth, S Maschek, B Sveinsson, F Eckstein, EHG Oei, GE Gold, BA Hargreaves. Five-minute knee MRI for simultaneous morphometry and T_2 relaxometry of cartilage and meniscus and for semiquantitative radiological assessment using double-echo in steady-state at 3T. *J Magn Reson Imaging*. 2018;47(5):1328-1341

SM Eijgenraam, L Utomo, DE Meuffels, SMA Bierma-Zeinstra, YM Bastiaansen Jenniskens, GJVM van Osch. Meniscal extrusion and degeneration during the course of osteoarthritis in the murine collagenase-induced osteoarthritis model. *J Orthop Res.* 2018;36(9):2416-2420

SM Eijgenraam, FAT Bovendeert, J Verschueren, J van Tiel, YM Bastiaansen-Jenniskens, MA Wesdorp, K Nasserinejad, DE Meuffels, J Guenoun, S Klein, M Reijman, EHG Oei. T_2 mapping of the meniscus is a biomarker for early osteoarthritis. 2019. *In press, Eur Radiol*

SM Eijgenraam, AS Chaudhari, M Reijman, SMA Bierma-Zeinstra, BA Hargreaves, J Runhaar, FWJ Heijboer, GE Gold, EHG Oei. Time-saving opportunities in knee osteoarthritis: structural imaging and T_2 mapping in the knee using a single 5-minute MRI scan. 2019. *In press, Eur Radiol*

SM Eijgenraam, J Verschueren, S Klein, DHJ Poot, SMA Bierma-Zeinstra, JA Hernandez Tamames, PA Wielopolski, M Reijman, EHG Oei. T_2 mapping of knee cartilage: multicenter multivendor reproducibility. *2019. Submitted for publication*

SM Eijgenraam, DE Meuffels, SMA Bierma-Zeinstra, M Reijman. Rationale and design of the STARR trial: Should a traumatic meniscal tear be resected; A randomized controlled trial. *2019. Submitted for publication*

SM Eijgenraam, MA Wesdorp, DE Meuffels, SMA Bierma-Zeinstra, EB Burger, YM Bastiaansen-Jenniskens, M Reijman. Traumatic meniscal tears are associated with meniscus degeneration. *2019. Submitted for publication*

Thank you!


Erasmus MC
Universitair Medisch Centrum Rotterdam


orthopedie
groot eindhoven


Stanford
MEDICINE


Nederlandse Vereniging
voor Arthroscopie


Smith+Nephew


ChipSoft


VREST
proving & improving competences


SPOMED


Guerbet


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RESEARCH SOCIETY
INTERNATIONAL


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OF RADIOLOGY


ZonMw