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].

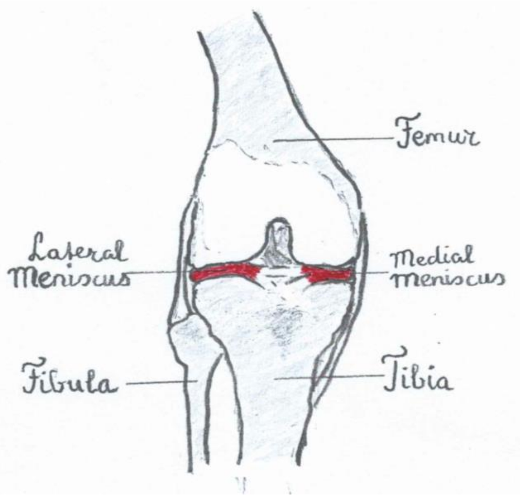

Figure 1. Anatomy of the human menisci. Right knee, frontal view, patella removed. Knee is slightly flexed. Medial and lateral menisci are highlighted in red. *Artwork by the author.*

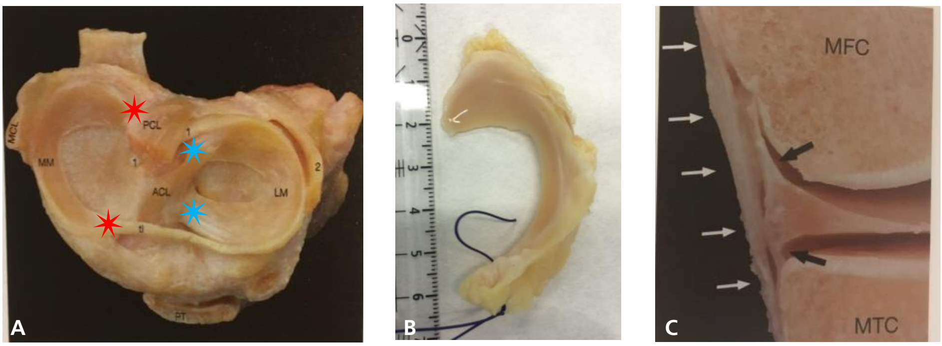

Figure 2. Attachments of the menisci. A) Left cadaveric knee joint, top view, femur removed. Note the difference in tibial attachments of meniscal roots between medial (red stars) and lateral (blue stars) meniscus. B) Medial meniscus, *ex vivo*, obtained during upper leg amputation in a 53-year-old male 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.*

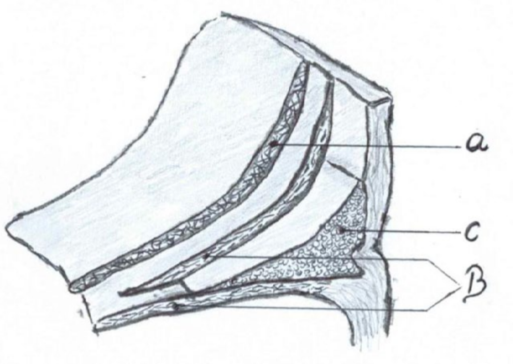

Figure 3. Cross-sectional view of the meniscus showing its collagen fiber configuration. A) Tightly woven superficial mesh layer. B) Radially oriented collagen fibers. C) Circumferentially oriented collagen fibers. *Artwork by the author.*

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].

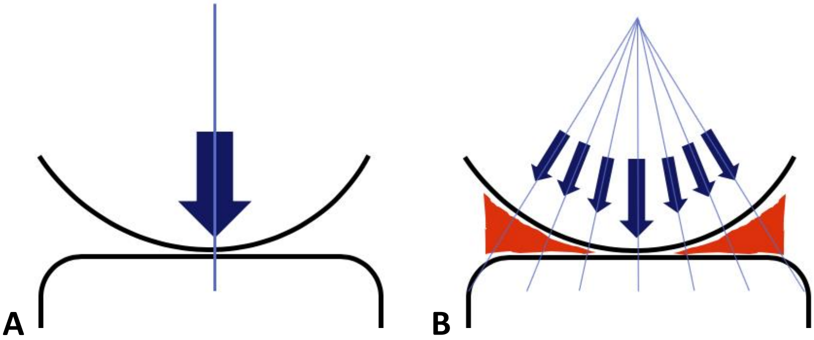

Figure 4. Biomechanical function of the meniscus. Schematic view of the knee joint in sagittal plane, in absence (A) and in presence (B) of the meniscus. The menisci, highlighted in red, distribute compressive load (blue arrows) and decrease contact stress force throughout the knee joint.

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?).

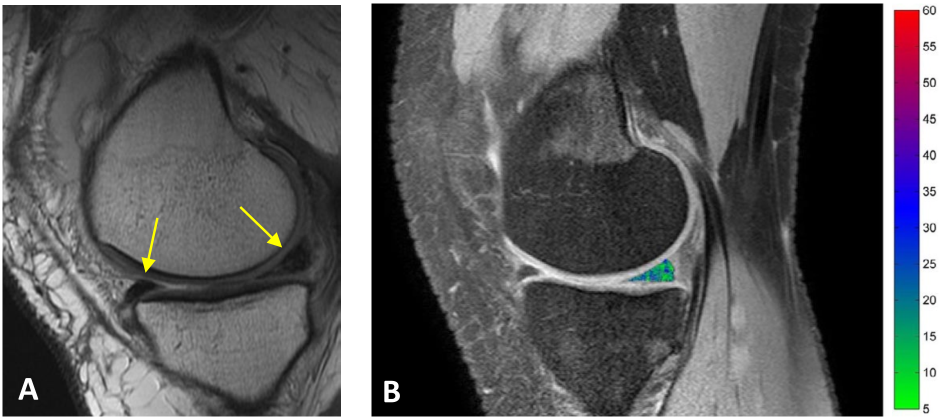

Figure 5. MR Imaging of the meniscus. A) Sagittal Proton-Density weighted image, medial compartment, anterior and posterior meniscal horns (yellow arrows) depicted as black triangles. B) Sagittal T_2 mapping image with colourmap of the posterior horn of the lateral meniscus.

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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