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.

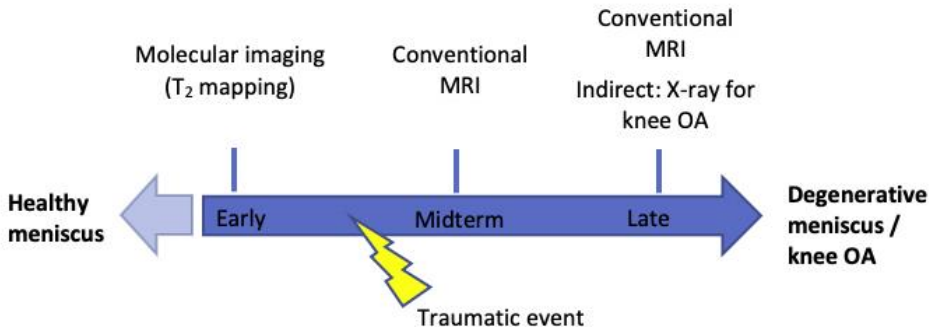

Figure 1. Schematic overview of the continuum theory of meniscal degeneration. During the course of the process from healthy meniscal tissue to meniscal degeneration (dark-blue arrow), optimal imaging techniques vary. Knee symptoms may occur in early phase, mid-term, late phase, or not at all. In this 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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