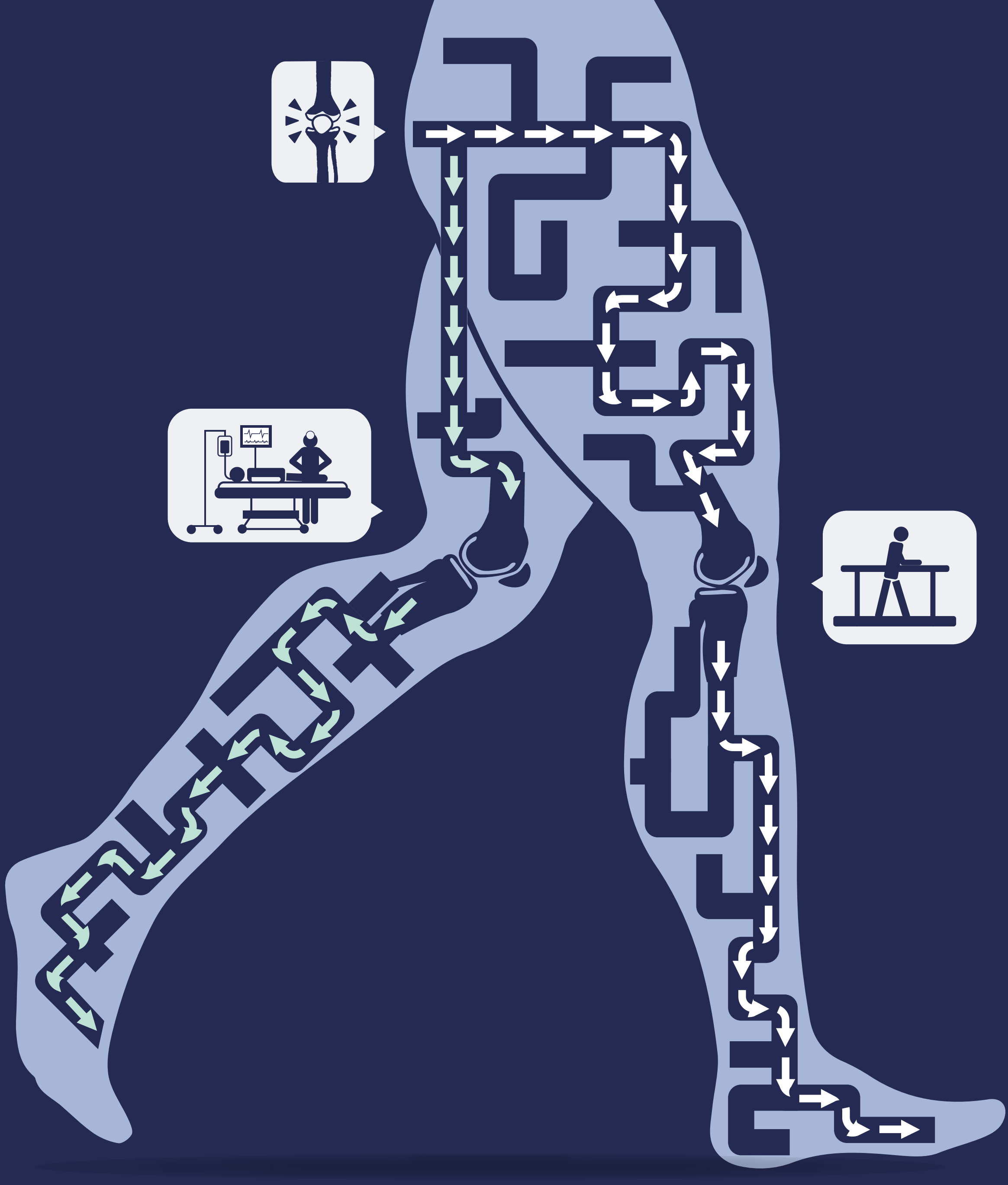

Clinical Decisions and Implications for Treatment of Anterior Cruciate Ligament Ruptures and Traumatic Meniscal Tears

Sabine van der Graaff

CLINICAL DECISIONS AND IMPLICATIONS FOR TREATMENT OF ANTERIOR CRUCIATE LIGAMENT RUPTURES AND TRAUMATIC MENISCAL TEARS

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Clinical Decisions and Implications for Treatment of Anterior Cruciate Ligament Ruptures and Traumatic Meniscal Tears

Klinische beslissingen en implicaties voor de behandeling van voorste kruisbandrupturen en traumatische meniscusscheuren

Proefschrift

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Chapter 1

Introduction and outline of this thesis

1

Traumatic knee injuries most frequently occur in young active patients during a sports-related trauma and have a major impact on patients' daily activity, sports, pain and quality of life. Common traumatic knee injuries in young active patients include the anterior cruciate ligament (ACL) and the menisci (Figure 1).

The ACL is one of the ligaments connecting the femur to the tibia and provides stability to the knee joint. The ACL originates from the intercondylar notch at the medial side of the lateral femoral condyle and consists of two bundles. It runs oblique through the intercondylar fossa and inserts at the medial tibial eminence.[1] ACL injury leads to a painful swollen knee with impaired function. Patients report complaints of instability and giving way. Objectively, there is anterior and rotational laxity of the knee joint.[2-4] An ACL injury has a major impact on a patient's life. Up to 25 years after ACL injury patients report lower knee-related quality of life compared to their peers.[5] About 35% of the patients is unable to return to their previous level of sport.[6] In the long term, having an ACL injury is a strong risk factor for the development of knee osteoarthritis (OA). The risk of developing knee OA is 4 times higher in an ACL deficient knee compared to a non-injured knee.[7]

The medial and lateral meniscus are wedged shaped fibrocartilaginous structures serving as weight distributor between the femur and the tibia and contributing to stability of the knee joint.[8] The menisci also contribute to shock absorption in the knee joint and reduce joint contact stresses.[9] Traumatic meniscal tears lead to swelling of the knee, pain and sometimes to locking of the knee joint and a limited range of motion. They limit patients in their daily activities and sports and can lead to loss of quality of life.[10, 11] Traumatic meniscal tears also increase the risk for knee OA on the long term. Having a meniscal tear increases the risk of developing knee OA by six times.[7]

As patients with both ACL injuries and traumatic meniscal tears are often in the midst of their working lives, these traumatic knee injuries have a high socioeconomic burden. This impact on society is further enhanced by the increased risk of knee OA in both ACL injuries and traumatic meniscal tears. OA is a prevalent disabling condition and the burden of this disease will rise the coming years.[12] With an incidence of 68.8 per 100,000 person-years for isolated ACL injuries and 61 per 100,000 person-years for meniscal injuries, these traumatic knee injuries play a significant role in the incidence of OA, leading to a major impact on society.[13, 14]

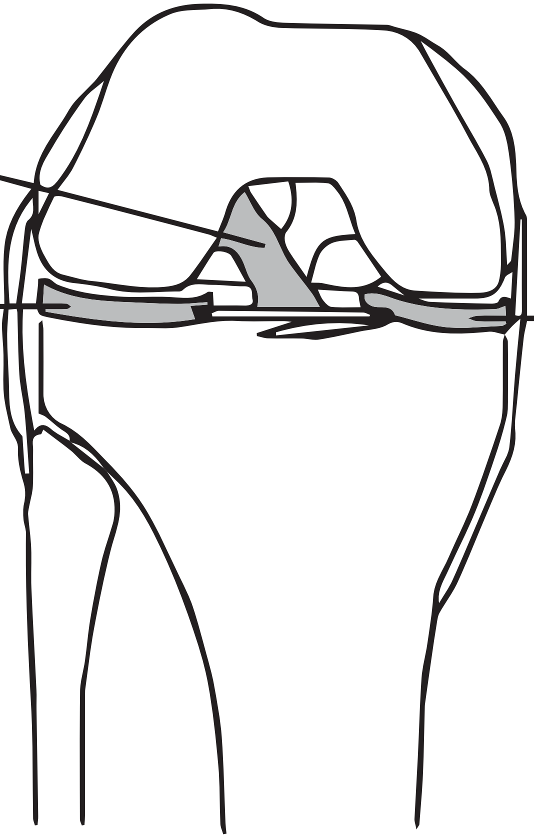

Figure 1. Knee joint (front view)

TREATMENT OF ACL INJURIES

For a long time, standard treatment of ACL injuries has consisted of surgical reconstruction of the ACL. During the last two decades of the twentieth century surgical reconstruction techniques were developed and improved to achieve the most optimal reconstruction. However, towards the end of the twentieth century there was increasing criticism of the standard surgical treatment for every patient with an ACL injury. In 2010 Frobell et al published the first randomized controlled trial (RCT) on the treatment of ACL injuries in young patients.[15] Patients were randomized to direct surgical ACL reconstruction or initial physical therapy. The results of this RCT showed that after two years there was no clinical difference between patients who were randomized to surgery and those randomized to physical therapy. Forty percent of the patients who started with physical therapy had an ACL reconstruction during follow-up. Also five-year follow-up showed no differences in clinical outcomes, indicating that for some patients with ACL injuries physical therapy can be a first line treatment.[16] Despite these results the number of ACL reconstructions increased over the years, with 75 ACL reconstructions per 100,000 person-years in 2014.[17] In 2021 Reijman et al published a second RCT on treatment of ACL injuries, showing that early ACL reconstruction had no clinical relevant difference compared to rehabilitation therapy with optional delayed ACL reconstruction at two-year follow-up.[18] In this RCT (the COMPARE trial), 50 percent of the patients who started with physical therapy had a delayed ACL reconstruction during two-year follow-up.

In choosing the best treatment option for the individual patient multiple aspects are important to consider. The optimal treatment should not only be effective, which means having the best clinical effect, but also cost-effective, providing value for money. Additionally, it should not be harmful, by leading to additional injuries to the knee joint. It is thought that persistent instability in patients with an ACL deficient knee increases the risk of additional meniscal injuries.[19] One of the reasons to perform ACL reconstructions shortly after trauma is to reduce instability and minimize the risk of new meniscal injuries. A recent systematic review showed that the existing evidence is too weak to conclude that non-operative treatment of ACL ruptures leads to more new meniscal tears compared to surgical treatment.[20] RCTs can investigate these different aspects, so the effectiveness, cost-effectiveness and chance for additional injuries. However, RCTs answer questions on group level. In clinical practice orthopaedic surgeons are searching for the best treatment for each individual patient. In the COMPARE trial half of the patients failed physical therapy and had to undergo a delayed ACL reconstruction. The question is why, when and which patients were unsuccessful with physical therapy and whether there are any prognostic variables. This aspect has not been thoroughly investigated before, especially not in an RCT study population. Ideally, we aim to predict which patients would benefit from surgery and which ones can effectively manage with physical therapy.

TREATMENT OF TRAUMATIC MENISCAL TEARS

Traumatic meniscal tears in young patients are usually treated surgically if possible through either a meniscal repair or a partial meniscectomy.[21, 22] Gaining insights lead to more focus on saving the meniscus, reducing long term degeneration in the knee joint.[22] Nevertheless, arthroscopic partial meniscectomy remains the most frequently performed orthopaedic surgery worldwide.[23-25] Yearly, approximately 30,000 meniscectomies are performed in the Netherlands, of which half in patients under 45 years old.[26] Over the years, many RCTs have been published on treatment of degenerative meniscal tears in older patients.[27-30] These studies showed that at group level, partial meniscectomy has no benefit compared to non-operative treatment. As a result, new clinical practice guidelines recommend initial non-operative treatment for older patients with degenerative tears.[31, 32] There is a lack of high quality RCTs investigating different treatments for traumatic meniscal tears in young patients.

As traumatic meniscal tears affect young people in the midst of their working life, they do not only affect quality of life but also have a high socioeconomic burden, including lost productivity and increased health care costs. Particularly for high-frequency surgeries as arthroscopic partial meniscectomy in young patients with traumatic meniscal tears it is important to assess their clinical effectiveness but also their cost-effectiveness in terms of health benefit gained relative to the associated costs. This can be evaluated in a cost-effectiveness analysis. In this type of analysis two treatments are compared for their effect on quality of life and the costs of gaining health benefit.

Traumatic meniscal tears increase the risk of early OA in a relative young knee.[7] One of the challenges in treating young patients with traumatic meniscal tears is minimizing the risk for posttraumatic OA. From multiple studies we learnt that removing the entire meniscus leads to early knee OA.[33] Therefore there is a tendency to save the meniscus.[22] Both surgical treatment options for a traumatic meniscal tear, arthroscopic partial meniscectomy and meniscal repair, increase the risk for knee OA.[34] Meniscal repair of traumatic meniscal tears may reduce the risk for OA compared to arthroscopic partial meniscectomy by 40 percent, but still is associated with a higher risk compared to the general population.[35] It is unknown whether operative and non-operative treatment of traumatic meniscal tears lead to a difference in early OA-related changes and whether we should take this into account when choosing the optimal treatment. Magnetic resonance imaging (MRI) is an important imaging tool for OA research, since it can visualize all structures of the knee joint involved in OA.[36] MRI can visualize different OA-related features in the knee joint, such as bone marrow oedema, cartilage defects and osteophytes.[36] Bone marrow oedema can also be related to an acute trauma of the knee joint. It can occur at the location of a direct trauma or may show typical patterns matching various indirect trauma mechanisms.[36, 37] Cartilage damage can also be related to both acute knee trauma and OA.

AIMS

Treatment of traumatic knee injuries in young patients should be based on high quality evidence from clinical trials. The aim of this thesis is to investigate the optimal treatment for both ACL injuries and traumatic meniscal tears in young patients, with a focus on clinical and economical aspects but also on the effects of treatment on potential additional damage or degeneration of the knee joint. This thesis elaborates on the results of the COMPARE trial, by investigating why, when and which patients need an ACL reconstruction. We also assess if delaying ACL surgery is safe in terms of additional meniscal injuries. Given the absence of high quality RCTs on the treatment of traumatic meniscal tears we have designed an RCT in young patients with traumatic meniscal tears to investigate the clinical effectiveness and cost-effectiveness of current treatment.

The aims for this thesis are:

1. To investigate why, when and in which patients' non-operative treatment of ACL injury fails. (Chapter 2)
2. To evaluate whether initial non-operative treatment of ACL injuries leads to more meniscal procedures. (Chapter 3)
3. To compare the clinical outcomes between arthroscopic partial meniscectomy and physical therapy in young patients with traumatic meniscal tears. (Chapter 4)
4. To evaluate the cost-effectiveness of arthroscopic partial meniscectomy in treatment of young patients with traumatic meniscal tears. (Chapter 5)
5. To identify posttraumatic and OA-related lesions on MRI in young patients with isolated traumatic meniscal tears. (Chapter 6)
6. To examine the presence of early degenerative changes on MRI 24 months after meniscal tears and compare these changes between arthroscopic partial meniscectomy and physical therapy. (Chapter 7)

OUTLINE

The challenge we aim to address in each patient with an ACL rupture is determining the optimal treatment for each individual at the right moment. Therefore, Chapter 2 investigates why, when and which patients fail non-operative treatment of ACL injury, by using data from the COMPARE trial. As evidence from high quality RCTs on additional meniscal injuries after ACL injury is lacking, Chapter 3 evaluates the number of meniscal procedures in operative and non-operative treatment of ACL injuries.

As mentioned earlier, high quality evidence on treatment of traumatic meniscal tears is lacking and therefore we performed an RCT in young patients with isolated traumatic meniscal tears. We randomized them between arthroscopic partial meniscectomy and non-operative treatment with optional delayed arthroscopic partial meniscectomy (STARR trial). Chapter 4 describes the clinical outcomes of this RCT after 24 months of follow-up. Since the optimal treatment of traumatic meniscal tears should not only be effective, but also cost-effective, Chapter 5 presents the results of a cost-effectiveness analysis of the STARR trial.

To gain more insight in the effect of isolated traumatic meniscal tears on the knee joint we studied MRIs of patients in the STARR trial. In Chapter 6 we identify posttraumatic and OA-related lesions on the MRIs of patients with isolated traumatic meniscal tears at baseline. To evaluate the effects of operative and conservative treatment of traumatic meniscal tears on degeneration of the knee joint Chapter 7 assesses the presence of degenerative changes in the knee joint in patients from the STARR trial at 24-month follow-up. Together these clinical, cost-effectiveness and radiological outcomes will contribute to a more evidence based approach of treating young patients with isolated traumatic meniscal tears.

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Chapter 2

Why, when, and in which patients non-operative treatment of anterior cruciate ligament injury fails: an exploratory analysis of the COMPARE trial

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ABSTRACT

Background

The optimal treatment strategy for patients with an anterior cruciate ligament (ACL) rupture is still under debate. Different determinants of the need for a reconstruction have not been thoroughly investigated before, especially not in a randomized controlled trial study population.

Purpose

To investigate why, when and which patients with an ACL rupture who initially started with rehabilitation therapy required reconstructive surgery.

Methods

In the COMPARE trial, 167 patients with an ACL rupture were randomized to early ACL reconstruction or rehabilitation therapy plus optional delayed ACL reconstruction. We conducted an exploratory analysis of a subgroup of 82 patients from this trial, who were randomized to rehabilitation therapy plus optional delayed ACL reconstruction. The reasons for surgery were registered for the patients who underwent a delayed ACL reconstruction. For these patients we determined International Knee Documentation Committee (IKDC), numeric rating scale (NRS) pain and instability question from the Lysholm questionnaire before surgery. To determine between group differences between the non-operative treatment and delayed ACL reconstruction group, IKDC and pain scores during follow-up were determined using mixed models and adjusted for sex, age and BMI.

Results

During two-year follow-up of the trial 41 of the 82 patients received a delayed ACL reconstruction after a median time of 6.4 months after inclusion (IQR 3.9-10.3). Most reconstructions occurred between three and six months after inclusion (n=17, 41.5%). Ninety percent of the patients (n=37) reported knee instability complaints as reason for surgery at the moment of planning surgery. Of these patients, 18 had an IKDC score below 60, 29 had a pain score of 3 or higher and 33 patients had knee instability complaints according to the Lysholm questionnaire prior to surgery. During follow-up, IKDC scores were lower and pain scores were higher in the delayed reconstruction group compared to the non-operative treatment group. Patients in the delayed reconstruction group had a significant lower age (27.4 versus 35.3 years, p=0.001) and higher pre-injury activity level compared to patients in the non-operative treatment group.

Conclusion

Patients who experienced instability complaints, pain during activity and had a low

perception of their knee function were unsuccessful with non-operative treatment. Most patients received a delayed ACL reconstruction after 3 to 6 months of rehabilitation therapy. At baseline, patients that required reconstructive surgery had a lower age and higher pre-injury activity level compared to patients that were not reconstructed.

2

INTRODUCTION

Finding out who needs which treatment at what moment is the challenge we try to solve after each anterior cruciate ligament (ACL) rupture. Currently, which treatment would be best for every patient, cannot be determined on a scientific basis and we do not know what treatment is successful in what situation. In a randomized controlled trial (RCT) comparing two different treatment strategies for ACL rupture, we found that early surgical reconstruction, compared to rehabilitation therapy with optional delayed reconstruction, resulted in improved clinical outcomes at two-year follow-up that were significant but of uncertain clinical importance.[1] This study (Conservative versus Operative Methods for Patients with ACL Rupture Evaluation (COMPARE) trial) showed that half of the patients who started with non-operative treatment had satisfactory clinical results and did not need a surgical reconstruction during the two-year follow-up period.[1] However, the other half of the patients failed non-operative treatment and received a delayed ACL reconstruction. In the current study, we are looking for the why, when and who in failing non-operative treatment. This has not been thoroughly investigated before, especially not in a RCT study population.

In most studies and guidelines, symptomatic instability complaints are an indication for an ACL reconstruction, if these complaints are not reduced after a physiotherapeutic guided exercise program or after adjustment of activity.[2-5] Nevertheless, despite many objective measures of knee stability, objectifying how a patients perceives the instability remains a challenge, especially during activities in daily living.[6] So, the existing instruments do not predict the necessity for a reconstruction. Functional outcome measures may give a better indication of which patients need an ACL reconstruction.[7]

Furthermore, few studies described the time between starting non-operative treatment and receiving an ACL reconstruction.[8, 9] The two existing RCTs described the average time to delayed ACL reconstruction, but timing for each individual patients has not been described yet.[1, 3] Investigating individual timing can give more insight in the distribution of time to delayed ACL reconstruction.

Therefore, the aim of the present study is to explore why, when and which patients with an ACL rupture who started with rehabilitation therapy were eventually reconstructed, using data of the COMPARE trial. In this exploratory analysis we evaluated which and how knee complaints, symptoms and Patient Reported Outcome Measures (PROMs) relate to the need for a delayed ACL reconstruction after failed non-operative therapy.

METHODS

Study design and patients

We used data of the COMPARE trial, a multicenter RCT that recruited patients with an acute ACL rupture at 6 hospitals in the Netherlands. The research protocol was approved by the Erasmus MC University ethics committee and the trial was registered with trial number NL2618 in the Dutch trial registry. In the COMPARE trial patients aged 18-65 years with an acute ACL rupture confirmed by MRI and physical examination were included. Main exclusion criteria were history of ACL injury and a bucket handle lesion of the meniscus with an extension deficit. Additional information about the recruitment process and exclusion criteria has been described in more detail in the paper about the COMPARE trial.[1]

Treatment

Patients were randomly assigned to early ACL reconstruction or rehabilitation therapy with optional delayed ACL reconstruction. Patients who were randomized to rehabilitation therapy started with a three months supervised physical therapy program as recommended by the Dutch ACL guideline.[5] In case of symptomatic instability complaints or the inability to reach a desired activity level, patients could receive an ACL reconstruction after a minimum of three months of rehabilitation therapy. Of the 167 included patients 82 were randomized to rehabilitation plus optional delayed ACL reconstruction. For the present study we restrict our analyses to the group of patients who were randomized to rehabilitation therapy with optional delayed ACL reconstruction.

Outcomes

The primary outcome of the COMPARE trial was the patients' perception of symptoms, knee function and ability to participate in sports activities as measured by the International Knee Documentation Committee (IKDC) subjective form score. The IKDC score ranges from 0 to 100, with 100 as optimal score. It is a validated and appropriate outcome measure to evaluate the recovery of patients with an ACL rupture.[10, 11]

In the COMPARE trial also, other validated questionnaires were used for secondary outcomes, including the Lysholm questionnaire. This is a validated outcome measure to evaluate the functional status of patients with an ACL injury.[12] As a reflection of experienced instability question 5 of the Lysholm score was used. This question asks "Do you experience instability of your knee?". Scores for this question range from 0 (experiencing instability with every step) till 25 (never experiencing instability).

Pain severity during activity in daily living was determined by a numeric rating scale (NRS) score ranging from 0 to 10 (0 is equivalent to no pain).

In the COMPARE trial patients filled out questionnaires at baseline and 3, 6, 9, 12 and 24 months after randomization. Last reported PROMs before surgery was determined for every patient.

For each of these patients we registered the reason for surgery during follow-up, as well as any patients' preference for a reconstruction.

Data analysis

We described patients from the 'rehabilitation plus optional delayed ACL reconstruction' group of the COMPARE trial in an 'as treated' analysis. In this post-hoc comparison this group is divided in 'non-operative treatment' and 'delayed ACL reconstruction'. The 'non-operative treatment' arm consists of patients who did not receive an ACL reconstruction during the two-year follow-up period. The 'delayed ACL reconstruction' group consists of patients who received an ACL reconstruction during two-year follow-up.

Distribution of time between inclusion and surgery is described for patients of the delayed ACL reconstruction group, as well as reasons for surgery.

To give an overview of PROMs scores before patients received a reconstruction, Venn diagrams were made with IKDC score, pain score (NRS) during activity and patient's experienced instability as separate categories. We evaluated how many patients had a score of: a low to moderate IKDC (0-60) (based on normative IKDC scores in men and women between 18 and 65 years[13]), pain score (NRS) during activity higher or equal to 3 (moderate to severe pain) and instability score on the Lysholm questionnaire lower or equal to 20 out of 25 (minimally experienced instability during athletics or other severe exertion). Lysholm score of 20 was selected to also identify patients with minimal instability complaints.

Venn diagrams were also made for both treatment groups at baseline, with similar categories.

To determine between group differences (non-operative treatment versus delayed ACL reconstruction) of IKDC and pain scores during follow-up we used mixed models. IKDC score and pain scores (NRS) during activity, at baseline, 3, 6, 9, 12 and 24 months, were used as dependent variables. The treatment group (non-operative or delayed ACL reconstruction) was used as independent variable. The interaction between follow-up and treatment group was added to the model as fixed factor. The analysis was adjusted for potential confounders: sex, age and Body Mass Index (BMI). Surgeon was added as random factor into the model, since the randomization was stratified for orthopedic surgeon. All six participating hospitals had one or two orthopedic surgeons performing

ACL reconstructions and all surgeons had a minimum of ten years' experience in performing ACL reconstructions.

RESULTS

Patients

Half of the patients (n=41) in the rehabilitation plus optional delayed ACL reconstruction group received an ACL reconstruction during the two-year follow-up. This resulted in 41 patients in both the non-operative treatment group and delayed ACL reconstruction group.

Baseline characteristics are shown in Table 1. At baseline, patients in the delayed ACL reconstruction group had a significant lower age, lower BMI and higher pre-injury Tegner score compared to patients in the non-operative treatment group. They also injured their ACL more often during sport.

Table 1. Baseline characteristics 'rehabilitation plus optional delayed ACL reconstruction' group

	Non-operative treatment	**Delayed ACL reconstruction**	**P value**
	(n = 41)	(n = 41)	
Age at inclusion, years	35.3 (11.2)	27.4 (8.7)	0.001
Male sex, n (%)	23 (56.1)	28 (68.3)	0.255
BMI (kg/m²)	26.0 (4.2)	24.0 (3.7)	0.023
Tegner pre-injury	6.6 (2.1)	7.6 (1.7)	0.017
Time between trauma and inclusion, days (median and IQR)	46.0 (31.5; 57.5)	36.0 (29.0; 47.0)	0.185
ACL injured during sport, n (%)	32 (78.0)	39 (95.1)	0.023
Lachman positive, n (%)	41 (100.0)	41 (100.0)	1.0
MRI baseline, n (%)			
• meniscal tear	21 (51.2)	16 (39.0)	0.249
medial meniscus	9 (22.0)	8 (19.5)	
lateral meniscus	9 (22.0)	3 (7.3)	
both	3 (7.3)	5 (12.2)	
• chondral damage	9 (22.0)	7 (17.1)	0.577
• medial collateral ligament	18 (43.9)	13 (31.7)	0.255

Data is presented as mean, standard deviation between parentheses, unless reported otherwise

2

Delayed ACL reconstruction group

Median time from inclusion in the COMPARE study to delayed ACL reconstruction was 6.4 months (interquartile range (IQR) 3.9-10.3 months). Figure 1 shows the distribution of the time to surgery in months. A majority of the patients (41.5%) underwent delayed ACL reconstruction between three and six months after inclusion (median of 3.8 months). One protocol violation occurred; 1 patient underwent ACL reconstruction 9 days after inclusion, because of a second opinion at a non-participating private medical center that recommended and performed surgery within two days.

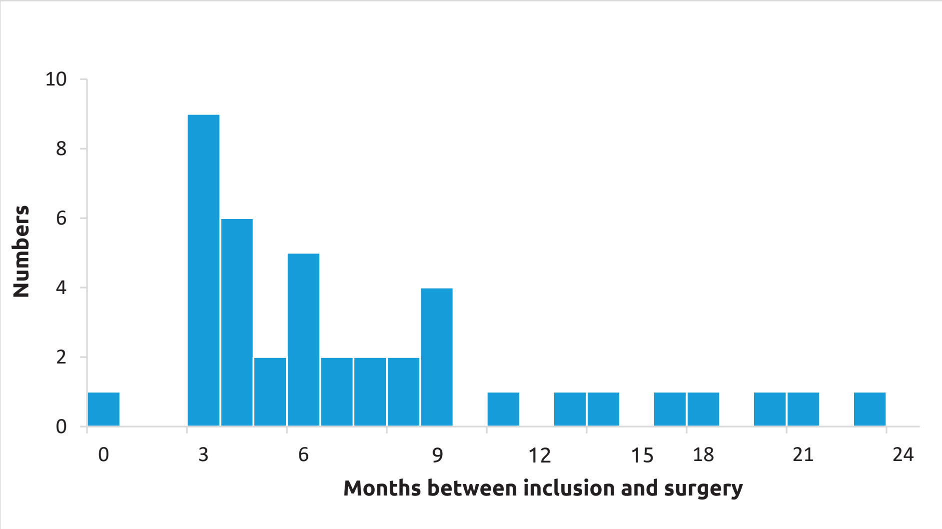

Figure 1. Time between inclusion and delayed ACL reconstruction
'Numbers' represents number of patients

A majority of the patients (n=37, 90.2%) reported knee instability complaints as reason for surgery. Of these patients 27% (n=10) had a strong preference for surgery. Of the remaining 4 patients, 2 had a strong preference for surgery without instability complaints, for 1 patient reason for surgery was not reported in the medical records and 1 patient went to another hospital where surgery was recommended (protocol violation mentioned before). In total 29.3% (n=12) of the patients had a strong preference for surgery.

Figure 2 shows PROMs scores of patients before they underwent a delayed ACL reconstruction. Of the 41 patients, 18 patients (43.9%) had a low to moderate IKDC score, 29 patients (70.7%) had a pain score of 3 or higher and 33 patients (80.5%) reported instability in the Lysholm questionnaire. In total 17 patients (41.5%) scored positive on all three items.

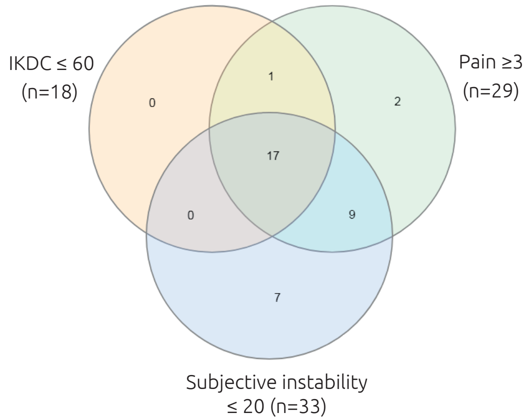

Figure 2. Delayed ACL reconstruction group (n=41) – PROMs before surgery

In the non-operative treatment group, at baseline 33 patients (80.5%) had a low to moderate IKDC score, 34 patients (82.9%) had a pain score of 3 or higher and 33 patients (80.5%) reported instability. In the delayed ACL reconstruction group the numbers of patients in these groups were respectively 27 patients (65.9%), 32 patients (78.0%) and 27 patients (65.9%), as shown in Figure 3.

Of the 33 patients who experienced instability complaints according to the last PROMs before surgery, 39.4% (n=13) had the same level of instability complaints at baseline and 27.3% (n=9) had no instability complaints at baseline but developed these during follow-up. The other patients had instability complaints at baseline that worsened (12.1% , n=4) or improved (21.2% , n=7) before surgery.

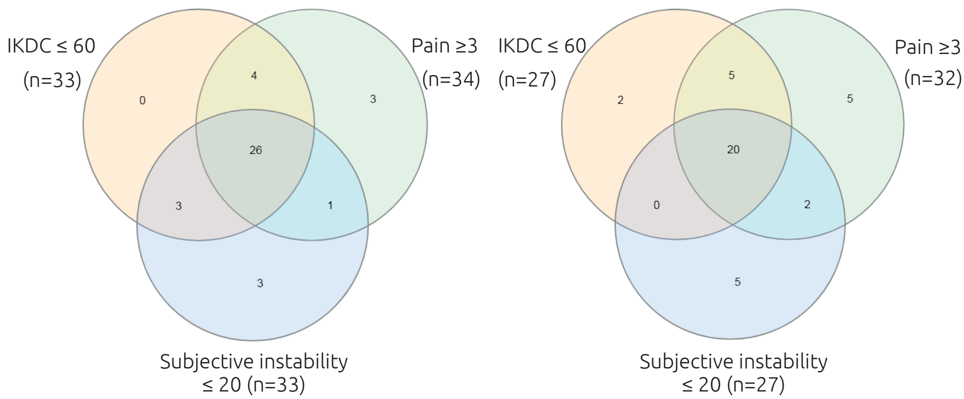

Figure 3. Baseline PROMs

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IKDC score over time

Figure 4 and Table 2 show the IKDC score during follow-up for both as treated groups. Patients of the delayed ACL reconstruction group were no longer included in the analysis from the moment onwards of ACL reconstruction. Before patients underwent delayed ACL reconstruction IKDC scores decreased, while patients that did not undergo ACL reconstruction showed an increase in IKDC score over time. At 3, 6, 9 and 12 months patients of the delayed ACL reconstruction group had a lower IKDC score compared to patients in the non-operative treatment group. Because of potential indication bias and a decrease in number of patients in the delayed reconstruction group, statistical analysis was not performed.

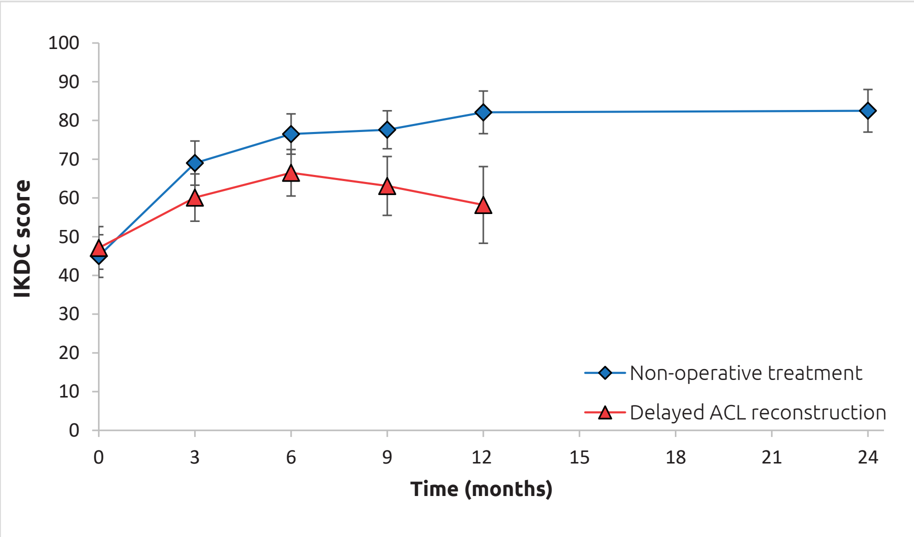

Figure 4. IKDC score over time
Bars represent 95% confidence intervals.

Table 2. 'As treated' analysis IKDC score (estimated IKDC*)

	IKDC baseline	IKDC 3 months	IKDC 6 months	IKDC 9 months	IKDC 12 months	IKDC 24 months
Non-operative treatment	45.0 (39.6; 50.5)	69.0 (63.3; 74.7)	76.5 (71.3; 81.7)	77.6 (72.7; 82.5)	82.1 (76.6; 87.6)	82.5 (77.0; 88.0)
Delayed ACL reconstruction**	47.1 (41.5; 52.6)	60.1 (54.1; 66.2)	66.5 (60.5; 72.5)	63.1 (55.5; 70.7)	58.2 (48.2; 68.1)	
Patients left	*41*	*36*	*22*	*13*	*7*	*0*
Between group difference	-2.0 (-10.0; 6.0)	8.9 (0.4; 17.4)	10.0 (1.9; 18.1)	14.6 (5.4; 23.7)	23.9 (12.4; 35.4)	

* values are presented as mean (95% confidence interval). Estimated IKDC adjusted for sex, age, BMI
** patients excluded after surgery

Pain during activity over time

Figure 5 and Table 3 show pain scores (NRS) during activity during follow-up for both as treated groups. Patients of the delayed ACL reconstruction group were excluded from the analysis after they were reconstructed. Patients of the delayed ACL reconstruction group had a higher pain score before they were reconstructed compared to the non-operative treatment group at 3, 6, 9 and 12 months of follow-up.

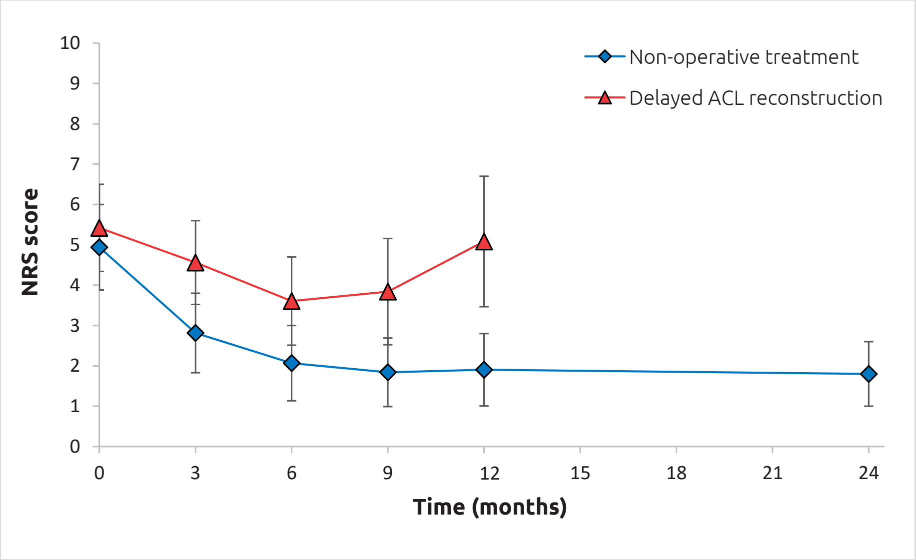

Figure 5. Pain during activity over time
Bars represent 95% confidence intervals.

Table 3. 'As treated' analysis NRS score (estimated NRS*)

	NRS baseline	NRS 3 months	NRS 6 months	NRS 9 months	NRS 12 months	NRS 24 months
Non-operative treatment	4.9 (3.9; 6.0)	2.8 (1.9; 3.8)	2.1 (1.1; 3.0)	1.8 (1.0; 2.7)	1.9 (1.0; 2.8)	1.8 (1.0; 2.6)
Delayed ACL reconstruction**	5.4 (4.4; 6.5)	4.6 (3.6; 5.6)	3.6 (2.5; 4.7)	3.8 (2.5; 5.2)	5.0 (3.5; 6.7)	
Patients left	*41*	*36*	*22*	*13*	*7*	*0*
Between group difference	-0.5 (-1.8; 0.8)	-1.7 (-3.0; -0.5)	-1.5 (-2.9; -0.2)	-2.0 (-3.5; -0.5)	3.2 (-5.0; -1.4)	

* values are presented as mean (95% confidence interval). Estimated IKDC adjusted for sex, age, BMI
** patients excluded after surgery

DISCUSSION

In this exploratory analysis of data of the COMPARE trial, we describe patients with an ACL injury who were unsuccessful with non-operative treatment. The symptoms these patients experienced before they received an ACL reconstruction were instability complaints, pain during activity and a low perception of their knee function indicated by a low IKDC score. Furthermore, we found that 41.5% of the patients received an ACL reconstruction after 3 to 6 months of rehabilitation therapy. Patients who failed non-operative treatment had a significant lower age and higher pre-injury activity level.

In our study most patients who were randomly assigned to rehabilitation therapy plus optional delayed ACL reconstruction received surgery after 3 to 6 months of rehabilitation therapy. A possible explanation for this peak is the presence of a strong pre-existing preference for surgery in 29.3% of the patients (n=12). Once the minimum period of 3 months of rehabilitation therapy according to the study protocol was completed, 9 of these patients (75%) underwent an ACL reconstruction within 3 months. A majority of the patients reported instability complaints as reason for surgical treatment. At baseline not all of these patients experienced instability complaints according to their Lysholm score. This indicates that symptomatic instability can also become a problem later on during the non-operative treatment period. After 1 year patients still received an ACL reconstruction in our study. Frobell et al reported similar results, in their study some patients even received surgery after 2 years of non-operative treatment because of new instability complaints.[3, 4]

At the last questionnaires before delayed ACL reconstruction, 43.9% of the patients experienced a low IKDC score, 70.7% reported moderate to severe pain during activity and 80.5% experienced some degree of symptomatic instability. Patients in the delayed reconstruction group reported these three symptoms more often compared to patients in the non-operative treatment group. Also during follow-up patients who eventually received surgery showed worsening IKDC and pain scores.

A majority of the patients received an ACL reconstruction after 3 to 6 months of non-operative treatment, but we also found that some patients developed instability complaints after a longer period of non-operative treatment and then received an ACL reconstruction. Furthermore, symptomatic instability complaints appear to be the main reason for patients to receive an ACL reconstruction, but patients also experience other symptoms, like a less optimal knee function (IKDC score ≤60) and pain during activity in daily living (NRS≥3).

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In our study symptomatic instability is the most important factor in receiving an ACL reconstruction after a period of non-operative treatment. These instability moments and the consecutive complaints could increase the risk for additional intra-articular damage in the ACL deficient knee, but the evidence for this hypothesis is not conclusive.[14] There is also no consensus about which level of instability complaints is clinically acceptable. Different objective measures of knee instability have been developed over the past years.[15, 16] These measures include different techniques to quantify knee instability, such as imaging techniques to detect rotational and anterior-posterior instabilities,[17] devices to measure knee laxity[18] and gait analysis.[19, 20] However, question is to what extent these measures correlate with the amount of instability that is experienced by the patient. Objectifying knee instability that patients experience during daily living still remains a challenge.[6] Laxity in the knee joint measured by different diagnostic techniques is different from instability experienced by the patient.

In our study we focused on instability experienced by the patient, since this is in on our opinion the best representation of how a patient experiences complaints in daily living. We found that patients with an ACL deficient knee report different levels of symptomatic instability and that even patients who rarely experienced knee instability also received an ACL reconstruction. It is possible that these patients have such a high desired activity level, that they do not accept any experienced knee instability. Furthermore, we showed that in the delayed ACL reconstruction group there were both patients who already had instability complaints at baseline and patients who did develop instability complaints during follow-up. This could indicate that symptomatic instability of the knee is fluid or that instability complaints change over time because of changes in activity level or changes in desired knee function.

Besides symptomatic instability, patient preference also plays an important role in the decision making process for surgery. This has evolved into more emphasis on shared decision making, which is defined as ”an approach where clinicians and patients share the best available evidence when faced with the task of making decisions, and where patients are supported to consider options, to achieve informed preferences”.[21] We tried to objectify as many of these parameters in our study and are further developing this area, where patients’ and physicians’ preferences are part of the decision making.

At baseline, patients in the delayed ACL reconstruction group had a significant lower age and higher pre-injury Tegner score compared to patients in the non-operative treatment group. Although we focused on PROMs at the moment of decision making for ACL reconstruction, these differences in baseline characteristics cannot be ignored. Activity level is probably the most important predictor for the necessity of an ACL reconstruction.[5] It is thought that the more a patient practices pivoting sports, the greater chance this

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patient needs a reconstruction.[22-25] In our study, patients who needed a reconstruction also had a younger age compared to the patients who were successful with non-operative treatment. This is similar to the study of Eitzen et al, that also found a younger age in patients who needed an ACL reconstruction.[7]

A limiting factor of this study is that deciding to perform an ACL reconstruction is a subjective decision of both the orthopedic surgeon and the patient. In this study we tried to objectify multiple aspects of this decision making, such as symptoms before surgery and time to surgery. However, it is hard to quantify and qualify all aspects of decision making. In clinical practice patients visit the surgeon with specific complaints and wishes, but these are not always comparable to the filled out questionnaires at each time point. We still aimed to cover all aspects of failing non-operative treatment, by investigating it from different perspectives, namely why, when and which patients needed an ACL reconstruction. Another limitation is the potential presence of recruitment bias in the COMPARE trial, because 41% of the eligible patients declined to participate in the trial. Furthermore, the relatively small sample sizes in each group led to a higher fragility index.

In conclusion, our current study provides more insight in patients who fail non-operative treatment after an ACL injury. To our knowledge, this is the first study that describes why, when and which patients with an ACL injury who started with non-operative treatment received an ACL reconstruction in an RCT set-up. We found that patients who received surgery experienced more knee instability, had lower IKDC scores and reported more pain during activity, compared to patients who followed a non-operative treatment successfully. Most patients failed non-operative treatment after 3 to 6 months of rehabilitation therapy, but some after a longer period of non-operative treatment. Patients who received surgery had a younger age and higher pre-injury activity level at baseline.

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Chapter 3

Meniscal procedures are not increased with delayed ACL reconstruction and rehabilitation: results from a randomised controlled trial

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ABSTRACT

Objective

To assess whether initial non-operative treatment of anterior cruciate ligament (ACL) ruptures with optional delayed ACL reconstruction leads to more meniscal procedures compared to early ACL reconstruction during two-year follow-up.

Methods

We compared the number of meniscal procedures of 167 patients with an ACL rupture, who either received early ACL reconstruction (n=85) or rehabilitation therapy plus optional delayed ACL reconstruction (n=82), participating in the COMPARE trial. Patients were aged 18 to 65 years (mean 31.3, SD 10.5), 60% male sex (n=100). We evaluated the presence and location of meniscal tears by baseline MRI. We analysed and compared how many patients per randomisation group had a meniscal procedure during follow-up in the ACL injured knee, adjusted for sex, BMI, age group and orthopaedic surgeon.

Results

At baseline 41% of the entire study population (69/167 patients) had a meniscal tear on MRI. During the two-year follow-up 25 patients randomised to early ACL reconstruction (29%, 25/85 patients) had a meniscal procedure, compared to 17 patients randomised to rehabilitation plus optional delayed reconstruction (21%, 17/82 patients) (risk ratio 0.67 with 95% confidence interval 0.40 to 1.12, p-value 0.12). Of these patients who received early ACL reconstruction (n = 82) and patients who received delayed ACL reconstruction (n = 41), 5% of the patients had an additional isolated meniscal procedure after ACL reconstruction. In patients who received no ACL reconstruction (n=41), 10% (n=4) had an isolated surgical procedure for a meniscal tear during the two-year follow-up period.

Conclusion

Initial non-surgical treatment of ACL ruptures followed by optional delayed ACL reconstruction does not lead to a higher number of meniscal procedures compared to early ACL reconstruction over a two-year follow-up period.

INTRODUCTION

Meniscal injury influences the fate of a traumatic knee significantly and complicates the recovery of the anterior cruciate ligament (ACL) injured knee. An ACL rupture has a high chance of concomitant meniscal injury which varies in different studies from 40 to 60 percent.[1-6] Patients with both an ACL rupture and a meniscal tear have a six fold increased risk for osteoarthritis of the knee, with the meniscal injury as the most contributing risk factor.[7] Furthermore, meniscal injuries associated with ACL ruptures can lead to additional complaints such as locking knee, limited range of motion, pain, swelling, and often require physiotherapy or surgical intervention.[8, 9]

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It is thought that persistent instability in patients with an ACL deficient knee increases the risk of additional meniscal injuries.[10] One of the reasons to perform ACL reconstructions shortly after trauma is to reduce instability and also to reduce the risk of new meniscal injuries. A recent systematic review showed that the existing evidence is too weak to conclude that non-operative treatment of ACL ruptures leads to more new meniscal tears compared to surgical treatment.[11] However, an exploratory analysis of the KANON trial suggested that early ACL reconstruction may reduce the risk of new medial meniscal damage after an ACL rupture.[12]

Since previous data, except the KANON trial, are not from randomised trials, they are not optimal to address the risk of additional meniscal injuries with non-operative treatment of ACL ruptures. Therefore we compared the number of meniscal procedures in a secondary analysis of the most recent and largest randomised controlled trial (RCT) that compared two different treatment strategies for ACL rupture: early ACL reconstruction compared to rehabilitation therapy plus optional delayed ACL reconstruction in case of persisting instability complaints or the inability to reach a desired activity level.[13] Our aim was to evaluate whether initial non-operative treatment of ACL ruptures followed by optional delayed ACL reconstruction leads to more meniscal procedures compared to early ACL reconstruction during two-year follow-up.

METHODS

Study design and patients

Data from the Conservative versus Operative Methods for Patients with ACL Rupture Evaluation (COMPARE) trial were used.[13] This is a multicentre RCT that recruited patients with an acute ACL rupture at 6 hospitals in the Netherlands. Patients aged 18-65 year with an acute complete primary ACL rupture (within two months after the initial trauma) confirmed by MRI and physical examination were included. Exclusion criteria were history of ACL injury of the contralateral knee, a dislocated bucket handle lesion of the meniscus with an extension deficit, presence of another disorder that affects the activity level of the lower limb or insufficient command of the Dutch language.

The COMPARE trial obtained ethics approval by the Erasmus MC University ethics committee and the trial was registered with trial number NL2618 in the Netherlands trial registry. Informed consent was obtained from each patient in the study. After informed consent was obtained and baseline measurements had been carried out, patients were randomised into one of the two treatment groups. Randomisation was central, using computer generated randomisation lists (block randomisation, with variable sizes of the blocks (2, 4 and 6), stratified by orthopaedic surgeon and age group (<30 and ≥30)).

Patient involvement

In the absence of an adequate patient association, we formed a panel of patients with rupture of the ACL to review and comment on our study. Our patient panel consisted of three patients with an ACL rupture. The trial set-up was discussed with the patient panel before the subsidy request was submitted. In collaboration with these patients, we templated our study protocol as much as possible to our routine follow-up periods and standard measurements. Since 2010, we have expanded our use of patient participation panels on a regular basis. We plan to disseminate the results of the study to the study participants.

Interventions

Patients were randomly assigned to early ACL reconstruction or initial rehabilitation therapy plus optional delayed ACL reconstruction. Patients randomised to early ACL reconstruction received ACL reconstruction within 6 weeks after randomization. Following surgery patients were referred to physical therapy for further rehabilitation, according to the Dutch ACL guideline.[14] Depending on the findings during the arthroscopy, meniscal surgery was performed during the ACL reconstruction. Patients randomly assigned to rehabilitation therapy started with a minimum of 3 months supervised physical therapy, also following the Dutch ACL guideline.[14] Exercises were focused on balance and proprioception. MRI findings were explained and if a symptomatic meniscal tear existed, arthroscopic meniscectomy or repair could be performed. After the period of rehabilitation therapy, patients could opt for an ACL reconstruction, in case of persistent instability complaints or the inability to reach a desired activity level, in consultation with the orthopaedic surgeon.

In total 167 patients were included and randomised, 85 in the early ACL reconstruction group and 82 in the rehabilitation therapy plus optional delayed ACL reconstruction group. Of the latter 41 patients received a delayed ACL reconstruction during two-year follow-up.

Outcome measures

The primary outcome was whether a meniscal procedure was performed during the two-year follow-up period (yes or no). For patients who underwent an ACL reconstruction, arthroscopic findings of the affected knee were systematically described in the surgical report according to the Dutch knee arthroscopy guideline.[15] When patients underwent a meniscal procedure without ACL reconstruction, arthroscopic findings were also reported. When a meniscal procedure was performed, one investigator (SG) extracted the location and technique of the procedure (meniscectomy or meniscal repair) from the surgical report. During the two-year follow-up all additional interventions, arthroscopies and meniscal procedures were registered. We registered whether a meniscal procedure was performed before ACL reconstruction, during ACL reconstruction or after ACL reconstruction.

All included patients underwent an MRI of the affected knee at baseline. MRIs were made on different MRI scanners with a magnetic field strength of 1.5 T or 3.0 T. We used the following MRI pulse sequences: sagittal, axial and coronal proton density turbo spin echo (TSE) sequence (slice thickness 3 mm); sagittal and axial T2-weighted TSE sequence with fat saturation (slice thickness 3 mm). We defined presence of a meniscal tear as a grade 3 meniscal tear. A grade 3 meniscal tear has signal changes on MRI that reach the articular surface of the meniscus and therefore is considered to be a full tear.[8] One investigator (SG) was trained by a musculoskeletal radiologist with 15 years of experience. This investigator assessed all baseline MRIs and reported whether patients had no meniscal tear, a medial or lateral tear or a tear in both menisci. The investigator consulted an orthopaedic surgeon (DM) in case the baseline MRI was inconclusive. Together they reached consensus on all MRIs.

Data analysis

The baseline characteristics of the patients were described according to the randomly assigned treatment. The presence and location of meniscal injuries as assessed on baseline MRI were also described for the as randomised treatment groups.

We presented the number of meniscal procedures in a flowchart (Figure 1) for the 'as randomised' groups and for each 'as treated' group: patients who underwent early ACL reconstruction, patients who followed rehabilitation therapy during two-year follow-up (no ACL reconstruction group) and patients who started with rehabilitation therapy and opted for a delayed ACL reconstruction during follow-up (delayed ACL reconstruction group).

We analysed whether patients had a meniscal procedure in the ACL injured knee during the 24-month follow-up period using a modified Poisson regression, adjusted for sex, BMI, orthopaedic surgeon and age group.[16, 17] Patients were analysed according to their randomisation group. Dependent variable was meniscal procedure (yes/no), independent variables were randomisation (early ACL reconstruction or rehabilitation plus optional delayed ACL reconstruction), BMI, sex, orthopaedic surgeon and age group (<30 and ≥30 years). In the COMPARE trial randomisation was stratified for orthopaedic surgeon and age group (<30 and ≥30 years), therefore we added these factors to the model. We presented the risk ratio (RR) for having a meniscal procedure during follow-up of rehabilitation therapy plus optional delayed ACL reconstruction compared to early ACL reconstruction together with its uncertainty (95% confidence interval (CI)).

RESULTS

Patients

Baseline characteristics are reported in Table 1. In the early reconstruction group, 3 patients did not receive an ACL reconstruction, because of tomophobia (fear of surgery) in 1 patient and a negative pivot shift test during surgery in 2 patients.

Meniscal injuries on MRI

At baseline 41% (n=69) of the patients in the study population had a meniscal tear. Eighteen percent (n=30 of 167 patients) had a medial meniscal tear, 12% (n=20 of 167 patients) had a tear in the lateral meniscus and 11% (n=19 of 167 patients) had both a medial and lateral meniscal tear. In the early reconstruction group and rehabilitation plus optional delayed ACL reconstruction group respectively 40% (n=34) and 43% (n=35) of the patients had a meniscal tear on baseline MRI, as shown in Table 1.

Meniscal procedures during follow-up

All meniscal procedures are reported in Figure 1. In both randomisation groups, 1 patient underwent a meniscal procedure before inclusion, but after the trauma when the ACL ruptured. During the two-year follow-up 25 patients in the early ACL reconstruction group (29%, 25/85 patients) had a meniscal procedure in the ACL injured knee, with 3 patients that had 2 meniscal procedures in the same knee at 2 time points during follow-up. In the rehabilitation plus optional delayed reconstruction group 17 patients (21%, 17/82 patients) had a meniscal procedure in the ACL injured knee during follow-up, with 3 patients that had 2 meniscal procedures in the same knee at 2 time points during follow-up. The RR for having a meniscal procedure during the follow-up period was 0.67 (95% CI 0.40 to 1.12, p-value 0.12) for rehabilitation plus optional delayed ACL reconstruction compared to early ACL reconstruction. The model is based on 165 patients, there were two missing values.

Table 1. Baseline characteristics

	Early ACL Reconstruction (n = 85)	Rehabilitation plus optional delayed ACL reconstruction (n = 82)
Age at inclusion, years	31.2 (10.3)	31.4 (10.7)
Male sex, n (%)	49 (57.6)	51 (62.2)
BMI (kg/m²)	24.3 (3.7)	25.0 (4.1)
Tegner pre-injury	7.0 (2.3)	7.1 (2.0)
Time between trauma and inclusion, days	38.0 (14.5)	41.0 (14.0)
ACL injured during sport, n (%)	76 (89.4)	71 (86.6)
Lachman positive, n (%)	85 (100.0)	82 (100.0)
Meniscal injury on baseline MRI*		
- **No meniscal injury, n (%)**	50 (58.8)	47 (57.3)
- **Meniscal tear, n (%)**	34 (40.0)	35 (42.7)
Medial meniscus	14 (16.5)	16 (19.5)
Lateral meniscus	11 (12.9)	9 (11.0)
Both	9 (10.6)	10 (12.2)

Data is presented as mean, with standard deviation in brackets, unless otherwise reported.
BMI = body mass index
ACL = anterior cruciate ligament
* 1 missing in early ACL reconstruction

In the patients who underwent early ACL reconstruction (n = 82), 23 meniscal procedures were performed during reconstruction (28%, 23/82). In the patients who were randomised to rehabilitation therapy but underwent delayed ACL reconstruction during follow-up (n = 41), 13 meniscal procedures were performed during reconstruction (32%, 13/41). In the patients who underwent no ACL reconstruction (n = 41), 4 meniscal procedures were performed during separate arthroscopies (10%, 4/41) and 1 patient had a second meniscal procedure after the first separate arthroscopy.

After early ACL reconstruction 4 meniscal procedures (5%, 4/82) were performed, compared to 2 procedures (5%, 2/41) after delayed ACL reconstruction. These procedures were performed because of new trauma or knee complaints during follow-up. All 6 meniscal tears were located in meniscus tissue that was seen to be damaged during initial ACL reconstruction.

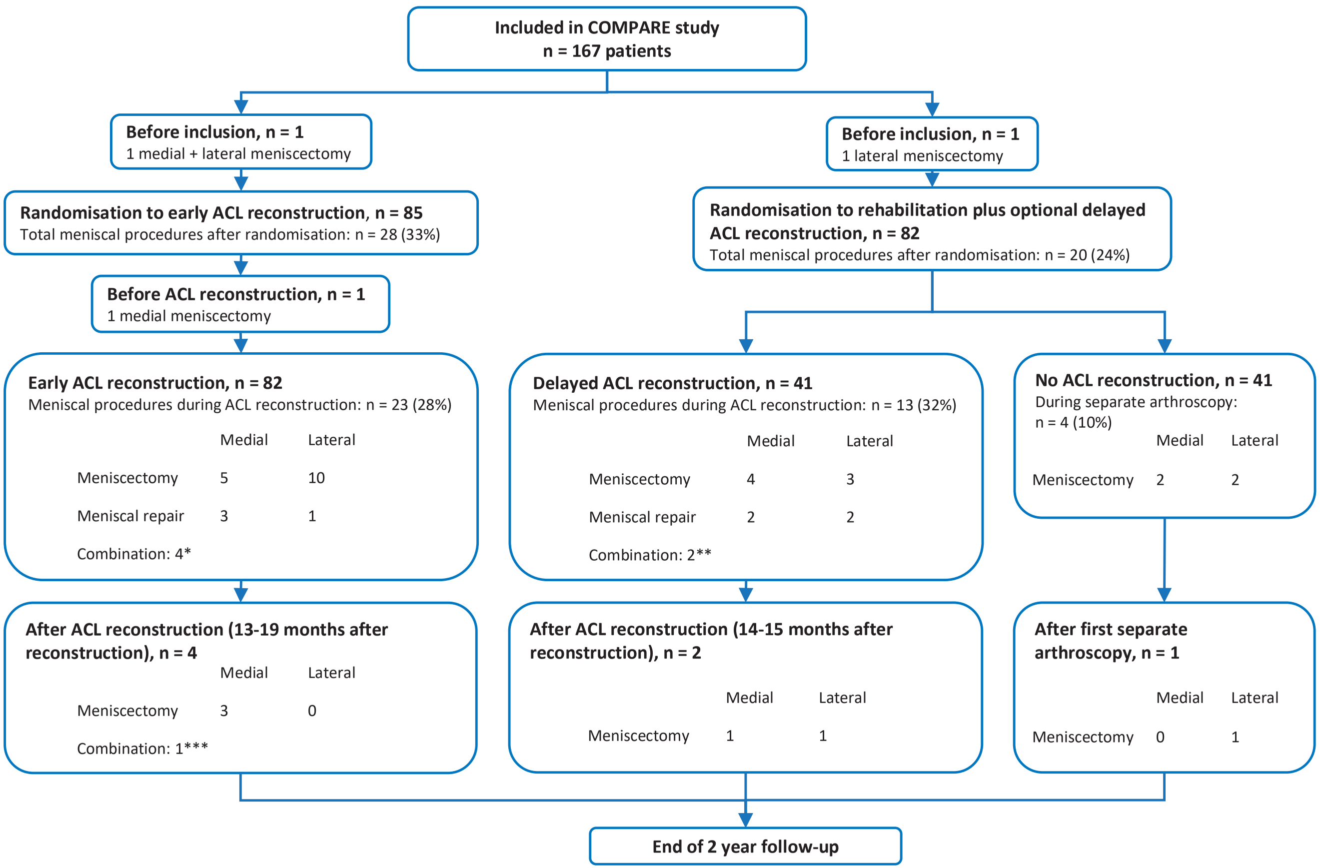

Figure 1. Meniscal procedures during follow-up.
*2 medial meniscectomy+lateral meniscectomy, 1 medial meniscal repair+lateral meniscectomy, 1 lateral meniscal repair+lateral meniscectomy.
** 1 medial meniscal repair+lateral meniscal repair, 1 medial meniscal repair+lateral meniscectomy.
*** 1 medial meniscectomy+lateral meniscectomy.
ACL, anterior cruciate ligament.

DISCUSSION

We found that the number of meniscal procedures in patients with an ACL rupture who were treated with rehabilitation therapy and optional delayed ACL reconstruction does not differ from patients who received early ACL reconstruction. After ACL reconstruction, in both treatment groups no new meniscal procedures were performed in parts of the meniscus other than the area that was already damaged as seen during ACL reconstruction.

We did not find that starting with non-operative treatment with optional delayed ACL reconstruction in patients with an ACL injury increases the risk for additional meniscal procedures in the first two years after trauma. This is in contrast to previous findings of studies that compared delayed and early ACL reconstruction.[4, 5, 18-21] A study of Granan et al analysed the Norwegian National Knee Ligament Registry. They concluded that the odds for meniscal tears after an ACL rupture increase with 1% every month that surgery is postponed.[4] Delaying ACL surgery is thought to increase the risk for additional meniscal damage because of an increase in knee instability episodes.[10] In a systematic review Sommerfeldt et al found low-evidence that recurrent instability after ACL rupture is associated with increased odds for medial meniscal lesions. All studies in this review were classified as 'high risk of bias' and patients undergoing non-operative treatment were under-represented. In a more recent systematic review Ekås et al found insufficient evidence that non-operative treatment increases risk for new meniscal tears.[11] Also in this review the included studies had a high risk of bias. A recent study of Snoeker et al (KANON trial) found a two times higher risk for medial meniscal tears in patients who were randomised to rehabilitation therapy treatment plus optional delayed ACL reconstruction after a five-year follow-up, but not after a two-year follow-up.[1, 12] Despite this higher risk for medial meniscal tears after five years, the number of meniscal surgeries during ACL reconstruction and thereafter in both treatment groups of the KANON trial did not differ after five years.[22] At two year follow-up, the KANON trial reported more meniscal surgeries compared to our study. This can be explained by the fact that in the KANON trial a part of the surgeries was counted per individual meniscus, so a meniscal surgery on both the medial and lateral meniscus was counted twice.

So far, the evidence for the risk of additional meniscal injuries with a delayed ACL reconstruction is inconclusive, mostly because of studies with poor methodology, like observational and register-based studies. However, the two randomised trials in this field with low risk of bias (KANON trial and our study) did not find a difference in the number of meniscal surgeries between early ACL reconstruction and non-operative treatment plus optional delayed ACL reconstruction after two years. Further follow-up of our study population will have to show whether the results will change at long term. Longer follow-up may lead to more meniscal surgeries, since with increasing time more traumatic moments can occur, meniscal injuries that are not treated during the study period may become symptomatic at a later time point and increasing age increases the risk for degenerative meniscal tears.

It is plausible that development of additional meniscal injuries after an ACL rupture is also dependent on the patients' activity level. It has been reported that higher activity levels can lead to a more than fourfold increase of the risk for additional knee injuries following ACL rupture.[23] Thus, a different post-injury activity level could also explain the differences between studies investigating secondary meniscal injuries after ACL rupture. Preinjury activity levels in the KANON were higher compared to preinjury activity levels in the COMPARE trial, but activity levels during follow-up were not reported in neither study.[1, 13] A lower post injury activity level may have influenced the development of meniscal injuries during the follow-up period in two ways. On the one side, a lower activity level may cause less meniscal injuries. On the other side, a lower activity level may also be the consequence of knee complaints because of a meniscal injury. Furthermore, the decision whether a patient needs a delayed ACL reconstruction or not is made by the orthopaedic surgeon and the patient. This introduces selection bias, the risk that the characteristics, like age and activity level, of both groups are not similar. These differences may have influenced the development of additional meniscal injuries. In both our study as well the KANON trial this may have biased the outcome.

All new meniscal tears that occurred after ACL reconstruction in both the early and delayed ACL reconstruction group were located in the same region of the meniscus as the part that was already damaged as seen during the ACL reconstruction. This can be explained either by an insufficient partial meniscectomy or meniscal repair during ACL reconstruction, or because no meniscal procedure was performed during ACL reconstruction. Another reason could be that the torn meniscal horn was already of lower quality because of histological changes.[24] These changes could also have played a role in the initial tearing of the meniscus. We reported in an earlier paper that meniscal tissue of traumatic tears has a higher degree of degeneration compared to healthy meniscal tissue, resulting in a meniscus that is more susceptible to tear.[24] So it could be that this part of the meniscus, although treated during ACL reconstruction, may get injured again more easily than other parts because of the histological changes.

In our study, only 10% (n=4) of the patients in the no ACL reconstruction group received meniscal surgery, although at baseline 46% (n=19) of the patients had a meniscal tear as seen on MRI. This indicates that during two-year follow-up only 21% (4/19) of the patients with a diagnosed meniscal tear had symptoms for which a meniscal surgery was performed. The majority of the patients in the no ACL reconstruction group had either no or mild knee complaints. Therefore, neither a knee arthroscopy nor meniscal procedure was performed. As reported earlier by Tornbjerg et al, the correlation between a meniscal tear and knee complaints is low, and thus, most patients with a meniscal tear are able to maintain a good knee function.[25] For traumatic meniscal tears, there is no consensus concerning the optimal treatment option, although there is limited evidence that small tears of the lateral meniscus can be left in situ and that other tears should be repaired.[26, 27] In our study, most patients in the no ACL reconstruction group did not receive meniscal surgery; however, it is undetermined yet whether these patients will develop meniscal complaints after a longer follow-up period.

The main strength of our study is that this is the second well performed RCT studying two different treatment strategies for ACL ruptures. Additionally, this study is further strengthened by the large study population. Another strength is that we compared meniscal tears between two different treatment strategies for ACL rupture in a randomised controlled set-up. This study therefore has low risk of bias compared to most previous studies.

A limitation of our study is that we did not perform an additional MRI at two-year follow-up. Therefore, we reported on meniscal procedures performed during follow-up and could not report all meniscal injuries after two years. Patients in the delayed reconstruction group received an ACL reconstruction because of knee symptoms and complaints, which may have influenced the number of meniscal procedures in this group. However, when the treatment groups are compared according to the randomly assigned treatment, the rehabilitation therapy plus optional delayed ACL reconstruction group did not receive more meniscal surgeries than the early ACL reconstruction group. Secondly, our study is a secondary analysis on a randomized trial and the COMPARE trial was not initially powered to answer the current research question. Thirdly, there may be recruitment bias in the COMPARE trial since 101 of the 282 eligible patients declined to participate in the study because of a strong preference for one of the treatment options (51 preferred surgery and 50 preferred non-operative treatment).[13] Because these preferences were equally divided, the results of our study would likely not have been different if all eligible patients had participated.

In the current study, numbers of meniscal procedures in the early ACL reconstruction and delayed ACL reconstruction group differ from the numbers reported in the previous paper of the COMPARE trial.[13] In the current paper we reported two additional meniscal procedures which were performed before inclusion in the study. In both the early and delayed ACL reconstruction group, one patient received a meniscal procedure before inclusion. In this paper we also assessed all baseline MRIs, while the previous paper of the COMPARE trial used the MRI reports from the different participating hospitals, resulting in different numbers of meniscal tears on baseline MRI.

In conclusion, in this study we did not find that initial non-surgical treatment of ACL ruptures followed by optional delayed ACL reconstruction leads to a higher number of meniscal procedures compared with early ACL reconstruction over a two-year follow-up period.

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Chapter 4

Arthroscopic partial meniscectomy versus physical therapy for traumatic meniscal tears in a young study population: a randomised controlled trial

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ABSTRACT

Objective

To compare outcomes from arthroscopic partial meniscectomy versus physical therapy in young patients with traumatic meniscal tears.

Methods

We conducted a multicentre, open-labelled, randomised controlled trial in patients aged 18-45 years, with a recent onset, traumatic, MRI-verified, isolated meniscal tear without knee osteoarthritis. Patients were randomised to arthroscopic partial meniscectomy or standardised physical therapy with an optional delayed arthroscopic partial meniscectomy after 3-month follow-up. The primary outcome was the International Knee Documentation Committee (IKDC) score (best 100, worst 0) at 24 months, which measures patients' perception of symptoms, knee function and ability to participate in sports activities.

Results

Between 2014 and 2018, 100 patients were included (mean age 35.1 (standard deviation 8.1), 76% male, 34 competitive or elite athletes). Forty-nine were randomised to arthroscopic partial meniscectomy and 51 to physical therapy. In the physical therapy group, 21 patients (41%) received delayed arthroscopic partial meniscectomy during the follow-up period. In both groups, improvement in IKDC scores was clinically relevant during follow-up compared to baseline scores. At 24 months mean (95% confidence interval) IKDC scores were 78 (71 to 84) out of 100 points in the arthroscopic partial meniscectomy group and 78 (71 to 84) in the physical therapy group with a between group difference of 0.1 (95% confidence interval: -7.6 to 7.7) points out of 100.

Conclusions

In this trial involving young patients with isolated traumatic meniscal tears, early arthroscopic partial meniscectomy was not superior to a strategy of physical therapy with optional delayed arthroscopic partial meniscectomy at 24-month follow-up.

INTRODUCTION

Arthroscopic partial meniscectomy is the most frequently performed orthopaedic surgery in the world.[1-3] Around 500,000 partial meniscectomies are performed annually in the United States, of which 40% in patients under 45 years.[3, 4] In middle age and older patients with chronic degenerative tears, multiple high level studies showed that partial meniscectomy has no benefit compared to non-operative treatment.[5-8] These studies led to new clinical practice guidelines making a strong recommendation against arthroscopic treatment and recommending initial non-operative treatment for older patients with degenerative tears.[9, 10]

Young patients with acute meniscal tears in previously healthy knees are usually offered surgery.[11, 12] There is a widespread belief that surgery is needed to diminish complaints such as locking and joint line pain but no high level trials have investigated arthroscopic partial meniscectomy compared with non-operative treatment.[12, 13] We conducted the first (to our knowledge) randomised controlled trial (RCT) in a young population (18 to 45 years) with traumatic meniscal tears in otherwise healthy knees, comparing the effectiveness of arthroscopic partial meniscectomy with physical therapy. The aim of our study was to investigate whether arthroscopic partial meniscectomy was superior to physical therapy in young patients with traumatic meniscal tears for IKDC score at 24-month follow-up.

METHODS

Study design

The Study of Traumatic meniscal tears: Arthroscopic Resection vs Rehabilitation (STARR) trial was an open-labelled, multicentre, parallel RCT. The trial was designed as a superiority study. Patients were recruited between August 2014 and November 2018 in 8 hospitals (1 university hospital and 7 non-university hospitals) in the Netherlands. The Erasmus MC University Medical Centre ethics committee approved the research protocol, and all patients gave written informed consent. The trial was registered in the Netherlands Trial Register prior to the inclusion of the first subject. Reporting follows the Consolidated Standards of Reporting Trials (CONSORT) guidelines.[14]

Patient involvement

Our patient panel consisted of 3 patients with a traumatic meniscal tear. The trial set up was discussed with a panel of people with acute knee injuries before the subsidy request was submitted. In collaboration with these patients, we made our study protocol as similar as possible to our usual clinical follow-up periods and standard measurements.

Since 2010 we have expanded our use of patient participation panels on a regular basis. We plan to disseminate the study results to study participants.

Patients and enrolment

Patients were recruited from outpatient clinics of the participating hospitals, after referral to the outpatient clinic either by the accident emergency department or by the general practitioner. Patients aged 18 to 45 years with a knee trauma in the previous 6 months (a specific incident after which knee complaints started) and a grade 3 meniscal tear on MRI were eligible for study participation. A grade 3 meniscal tear has signal changes on MRI that reach the articular surface of the meniscus and therefore is considered to be a full tear.[15] Exclusion criteria were: a locked knee (i.e. when the patient was unable to fully extend or flex the injured knee, confirmed by clinical exam), a meniscal tear that was suitable for suture repair based on MRI findings[16], a concurrent rupture of the anterior or posterior cruciate ligament, radiographic signs of osteoarthritis in the index knee (Kellgren Lawrence[17] grade 2 or higher), disabling comorbidity, or insufficient command of the Dutch or English language. Patients could have minor cartilage damage, which was not visible on radiographs. Eligible patients received oral and standardized written trial information.

Randomisation and allocation concealment

Following informed consent and baseline measurements, patients were randomised into one of the two treatment groups in a 1:1 ratio. Randomisation was stratified for participating orthopaedic surgeon. The enrolment personnel contacted one researcher (not otherwise associated with the trial) who allocated treatment arms using computer-generated random numbers (central randomisation). The type of randomisation was stratified balanced block randomisation. Treatment arms were allocated in block sizes varying from 2 to 6. During the interim analysis and the final analysis the statistician was blinded for treatment allocation.

Interventions

Arthroscopic partial meniscectomy

Arthroscopy was scheduled within 6 weeks of randomisation. When the meniscal tear was considered not suitable for suture repair on baseline MRI, but turned out to be suitable for suture repair during the arthroscopy based on perioperative findings, the orthopaedic surgeon was allowed to suture the ruptured meniscus. All participating orthopaedic surgeons normally performed at least 50 knee arthroscopies annually. All costs of surgery were covered by patients' health insurance. Postoperatively patients were treated according to routine clinical practice and the Dutch national guidelines, not all patients were actively referred to physical therapy but they were at liberty to do so.[18]

Physical therapy

Patients were referred to a physical therapist for an individual standardised physical therapy program lasting at least 3 months. This exercise program was developed by an expert panel consisting of experienced orthopaedic surgeons, sport physicians and physical therapists, based on clinical practice and available evidence.[18, 19] The program consisted of three phases: I) reducing knee effusion; II) optimising range of motion (a) and restoring coordination and muscle function (b); III) stimulating activities in daily living and return to sport. See Appendix 1 for a detailed description of the exercise program. The exercises were tailored to the individual. The frequency of physical therapy sessions was determined by the physical therapist, depending on the functional level of the patient and the patients' knee status. Patients' progress and compliance was actively monitored by the investigator and therapist. Patients also received a home exercise program (Appendix 1). Pain was handled using regular pain medication, starting with paracetamol, supplemented with non-steroid anti-inflammatory drugs (NSAIDs) if necessary. All costs of physical therapy were covered; financial arrangements in this context were established with health insurance companies. After the 3 months of physical therapy if they had persistent knee complaints, patients could opt for surgery, in consultation with the orthopaedic surgeon.

Outcome measures

The primary outcome was the IKDC score after 24-month follow-up. The IKDC score measures the patient's perception of symptoms, knee function and ability to participate in sports activities. IKDC score ranges from 0 to 100, where 100 is the optimal score. It is a widely used and validated patient reported outcome measure to evaluate the recovery of patients with meniscal injuries.[20]

Secondary outcomes were the Knee Injury and Osteoarthritis Outcome Score (KOOS), knee pain in rest and during activity (numeric rating scale (NRS)), Lysholm, Western Ontario Meniscal Evaluation Tool (WOMET), sporting activity level (Tegner score) and satisfaction with knee function. KOOS consists of five subscales; pain, symptoms, activities of daily living (ADL), sports and quality of life (QoL) and ranges from 0 to 100, with 100 being the optimal score.[21] NRS-pain ranged from 0 to 10, where 0 represented no pain. Lysholm ranges from 0 to 100, with 100 being the optimal score.[22] WOMET ranges from 0 to 100, where 100 is the optimal score.[23] WOMET is validated and reliable for assessing health related quality of life in patients with meniscal pathology.[24] The Tegner score ranges from 0 to 10, with 10 being the highest activity score.[22] Satisfaction ranged from 0 to 100, with 100 representing optimal satisfaction (visual analogue scale). Other secondary outcomes were serious adverse events (complications and re-interventions), which were recorded during patient visits to the outpatient clinic and retrieved from the patient records.[25]

Patients were seen at the outpatient clinic of the participating hospital at baseline and 12 and 24 months after randomisation. Patients completed all questionnaires digitally at 0, 3, 6, 9, 12 and 24 months, except for the KOOS and Lysholm questionnaire. The KOOS questionnaire was filled in at 0 and 24 months, the Lysholm questionnaire was filled in at 0, 12 and 24 months. Study data were collected and managed using GemsTracker electronic data capture tools hosted at Erasmus MC.[26]

When we calculated the sample size, no studies on minimal clinically important difference (MCID) for the IKDC score were available. We based our initial sample size calculation on detection of a difference with an effect size of 0.5 in favour of the arthroscopic partial meniscectomy group compared to the physical therapy group, with 80% power and a two-sided type I error of 5%. To allow for a potential loss to follow-up of 15% in two years and to compensate for per-operative conversions from meniscectomy to meniscal repair (estimated 5% in the arthroscopy group), the target sample was set to 158 patients (79 arthroscopic partial meniscectomy, 79 physical therapy).

During a planned interim report for the grant supplier, we had a lower loss to follow-up rate than anticipated. In the meantime a MCID for the IKDC score of 13.9 in knee injury patients had been published.[27] Based on a SD of 16.2 for this score at baseline in our study population so far, and based on the feasibility of recruitment in a reasonable time period, we agreed with the grant supplier on adjusting the sample size to 100 patients (50 arthroscopic partial meniscectomy, 50 physical therapy). As even with a much higher SD of 22 we still could detect a difference of 13.9 points with the same amount of loss to follow-up as initially anticipated. We reported the alteration in sample size in the trial register.

Statistical analysis

In the primary analysis, patients were analysed according to their randomisation group. To answer our primary research question, we used a linear regression model with IKDC score after 2 years as dependent variable, adjusted for baseline IKDC, randomisation and surgeon. We checked the following model assumptions: linearity, multicollinearity, homoscedasticity and normality and independence of residuals in the linear regression model. None of the assumptions were violated. To estimate the IKDC scores at baseline, 3, 6, 9 and 12 months, we used a linear mixed model to evaluate the between group difference in IKDC score, as indicated by the interaction between time point and randomised allocation. IKDC scores at baseline, 3, 6, 9, 12 and 24 months follow-up were used as dependent variable. Randomised allocation, follow-up period and interaction between randomised allocation and follow-up period (multiplication of randomisation and follow-up period as interaction term) were added to the model as fixed factors. Orthopaedic surgeon, used as stratum in the randomisation procedure, was added into the model as random factor. The covariance structure was modelled as unstructured. The model was estimated using the Restricted Maximum Likelihood (REML). We checked the following model assumptions: linearity, homoscedasticity and normality of residuals. None of the model assumptions were violated. In the secondary analysis, we analysed between group difference at 24 months in KOOS, NRS-pain, Lysholm, WOMET, satisfaction with knee function and Tegner, by using a linear mixed model as reported for the primary analysis. In all analyses, statistical significance was set at the two-sided .05 level.

RESULTS

Patients

During the study period, 100 patients were included of the 196 who were eligible. Forty-nine patients were randomised to arthroscopic partial meniscectomy and 51 patients to physical therapy (see Figure 1 and Table 1). Final follow-up was completed for 91% of all included patients. Our study population included 34 competitive or elite athletes with a Tegner score of 8 or higher.

Six patients (12%) of the arthroscopic partial meniscectomy group received no surgical treatment; in 4 patients' complaints had resolved before surgery, 1 patient withdrew from the study and 1 patient could not be reached. In 4 patients (8%) in the surgical group, the surgeon decided during surgery to perform meniscal repair instead of partial meniscectomy, based on arthroscopic findings. Twenty patients in the surgery group (42%) had one or more physical therapy sessions in the first three months after inclusion, median of 5.0 sessions, IQR 2.0 to 8.0.

In the physical therapy group, the median number of physical therapy sessions was 8.5 per patient (interquartile range 4.0 to 12.0). Twenty-one patients (41%) of the physical therapy group underwent a delayed arthroscopic partial meniscectomy during the follow-up period in consultation with the orthopaedic surgeon, because of persistent complaints. The time between randomisation and delayed arthroscopic partial meniscectomy ranged from 3 to 21 months with a median duration of 5.5 months.

Table 1. Baseline characteristics

	Arthroscopic partial meniscectomy (n = 48)	Physical therapy (n = 51)
Age at inclusion, years	34.1 (8.6)	35.6 (7.5)
Male sex, n (%)	37 (77)	38 (75)
BMI (kg/m²)	25.5 (4.2)	26.1 (4.6)
Tegner pre-injury[a]	6.5 (2.2)	6.4 (2.0)
Time between trauma and inclusion, days (median (IQR))	88 (48-150)	91 (58-149)
IKDC score[b]	46 (16)	47 (18)
KOOS score[c]		
pain	54 (20)	60 (21)
symptoms	56 (20)	63 (18)
ADL	61 (22)	69 (22)
sport	30 (25)	35 (29)
QoL	34 (18)	36 (18)
NRS-pain rest[d]	3.9 (2.5)	2.9 (2.8)
NRS-pain activity[d]	6.6 (2.4)	6.2 (2.4)
Lysholm score[e]	67 (18)	70 (18)
WOMET score[f]	38 (18)	43 (19)
Meniscus injured during, n (%)		
sport	27 (56)	27 (53)
daily activities	5 (10)	11 (22)
work	10 (21)	8 (16)
other	5 (10)	5 (10)
Meniscal tear baseline MRI, n (%)		
medial meniscus	31 (65)	35 (69)
lateral meniscus	16 (33)	14 (27)
medial + lateral meniscus	1 (2)	2 (4)

Data is presented as mean with standard deviation in brackets unless otherwise reported. Some values of the arthroscopic partial meniscectomy group are known for 47 patients instead of 48.
a The Tegner scores ranges from 0 to 10, with higher scores indicating a higher activity level.
b The IKDC score ranges from 0 to 100, with higher scores indicating less symptoms and a higher patient's perception of knee function and ability to participate in sports activities.
c The Knee Osteoarthritis Outcome Score ranges from 0 to 100, with higher scores indicating less pain and knee symptoms, less problems with activities of daily living (ADL) and sport and a better quality of life (QoL).
d The Numeric Rating Scale (NRS) for pain ranges from 0 to 10, with higher scores indicating more pain.
e The Lysholm score ranges from 0 to 100, with higher scores indicating less knee symptoms and higher levels of functioning.
f The Western Ontario Meniscal Evaluation Tool (WOMET) normalized score ranges from 0 to 100, with higher scores indicating a higher health-related quality of life.

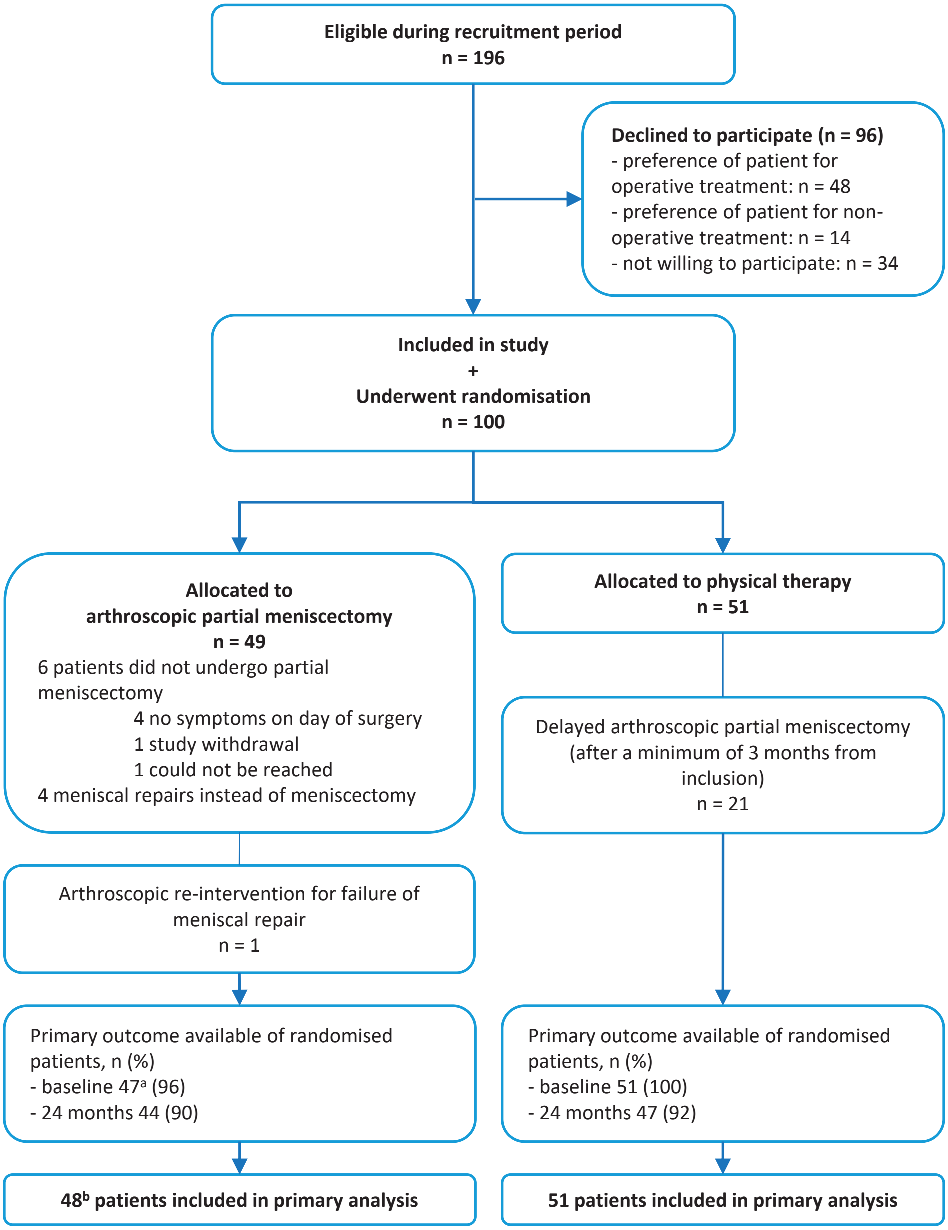
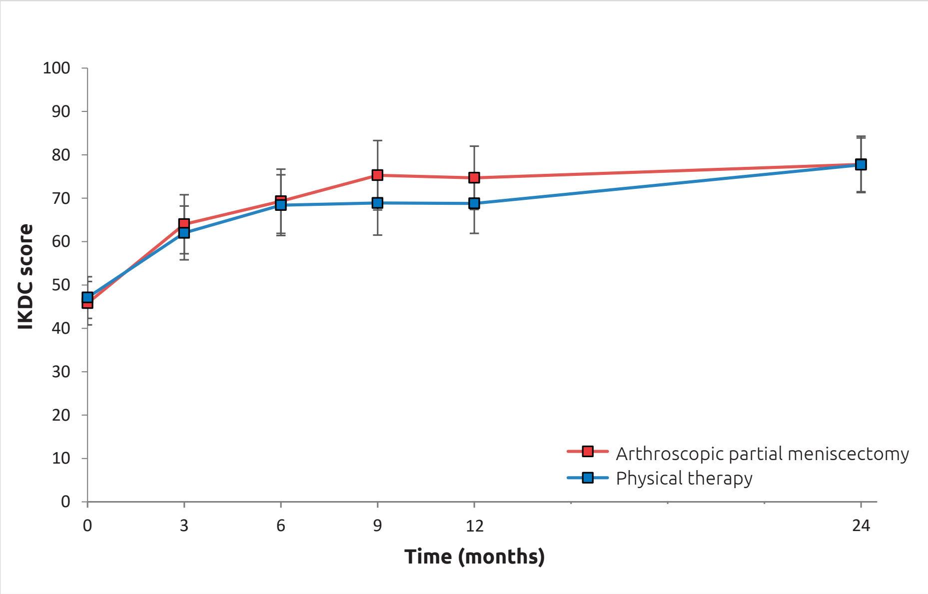


Figure 1. Flowchart
a minus 2 baseline questionnaires, 1 because of study withdrawal and 1 was incomplete
b minus 1 study withdrawal, who had no available data

Primary outcome

We did not find that arthroscopic partial meniscectomy is superior to physical therapy in IKDC score at final follow-up of 24 months (between group difference 0.1; 95% confidence interval -7.6 to 7.7; p-value 0.99). Both groups improved in IKDC score during the 24-month follow-up period (Figure 2). The change in IKDC score over the follow-up period and the between group differences during the different time points are shown in Figure 2.



	baseline	3 months	6 months	9 months	12 months	**Primary outcome 24 months**
Arthroscopic partial meniscectomy (n=48)	46 (41 to 51)	64 (57 to 71)	69 (62 to 77)	75 (67 to 83)	75 (67 to 82)	**78 (71 to 84)**
Physical therapy (n=51)	47 (42 to 52)	62 (56 to 68)	68 (61 to 75)	69 (62 to 76)	69 (62 to 76)	**78 (71 to 84)**
Between group difference[a]		2.0 (-5.8 to 10.0)	1.0 (-8.0 to 10.0)	6.3 (-3.4 to 16.0)	5.9 (-2.9 to 14.8)	**0.1 (-7.6 to 7.7)**
Primary outcome available, %	*98*	*77*	*70*	*63*	*75*	*91*

Figure 2. Estimated IKDC score[a] for as randomised analyses per measurement period
a 3, 6, 9 and 12 months: adjusted for surgeon, 24 months: adjusted for baseline IKDC, randomisation and surgeon
Error bars represent 95% confidence intervals. Table: 95% confidence interval in brackets. IKDC score ranges from 0 to 100, with higher scores indicating less symptoms and a higher patient's perception of knee function and ability to participate in sports activities.

Secondary outcomes

We did not find that arthroscopic partial meniscectomy was superior to physical therapy at 24 months in KOOS, NRS-pain, Lysholm, WOMET, Tegner and satisfaction with knee function (see Table 2). All data for the secondary outcomes at each time point are in Appendix 2.

Table 2. Secondary outcomes* for as randomised analyses 24 months follow-up

	Arthroscopic partial meniscectomy n = 48	Physical therapy n = 51	Between group difference
KOOS[a]			
pain	86 (79 to 92)	84 (77 to 90)	1.9 (-5.7 to 9.6)
symptoms	82 (75 to 88)	81 (75 to 88)	0.5 (-6.6 to 7.5)
ADL	92 (87 to 98)	89 (84 to 94)	2.8 (-3.3 to 8.9)
sport	70 (61 to 80)	69 (60 to 79)	0.8 (-12.5 to 14.0)
QoL	67 (59 to 75)	66 (58 to 74)	1.4 (-9.3 to 12.0)
NRS-pain rest[b]	1.2 (0.4 to 1.9)	1.2 (0.5 to 2.0)	-0.1 (-0.8 to 0.7)
NRS-pain activity[b]	2.8 (1.9 to 3.7)	2.4 (1.5 to 3.3)	0.4 (-0.8 to 1.5)
Lysholm[c]	89 (85 to 94)	88 (84 to 93)	-1.0 (-6.2 to 4.1)
WOMET[d]	72 (64 to 80)	76 (68 to 84)	-3.8 (-13.8 to 6.2)
Tegner[e]	5.4 (4.7 to 6.1)	5.0 (4.4 to 5.7)	0.3 (-0.6 to 1.3)
Satisfaction with knee function[f]	72 (64 to 80)	70 (62 to 78)	1.5 (-9.3 to 12.3)

Data is presented as adjusted mean estimate with 95% confidence interval in brackets.
* adjusted for surgeon
a The Knee Osteoarthritis Outcome Score ranges from 0 to 100, with higher scores indicating less pain and knee symptoms, less problems with activities of daily living (ADL) and sport and a better quality of life (QoL).
b The Numeric Rating Scale (NRS) for pain ranges from 0 to 10, with higher scores indicating more pain.
c The Lysholm score ranges from 0 to 100, with higher scores indicating less knee symptoms and higher levels of functioning.
d The Western Ontario Meniscal Evaluation Tool (WOMET) normalized score ranges from 0 to 100, with higher scores indicating a higher health-related quality of life.
e The Tegner scores ranges from 0 to 10, with higher scores indicating a higher activity level.
f Satisfaction with knee function is measured using a visual analogue scale ranging from 0 to 100, with higher scores indicating a higher patients' satisfaction with their knee function.

Serious adverse events (SAEs)

The number of SAEs is presented in Table 3. In both groups, 1 patient underwent an arthroscopic intervention for a meniscal tear in the contralateral knee. In the arthroscopic partial meniscectomy group, 1 patient underwent an additional arthroscopic intervention because of failure of the meniscal repair. In the patients who underwent delayed arthroscopic partial meniscectomy, 1 patient was found to have an anterior cruciate ligament rupture, which was discovered during arthroscopy and was not visible on the baseline MRI. This anterior cruciate ligament rupture was reconstructed at 13 months follow-up.

Table 3. Serious adverse events

	Arthroscopic partial meniscectomy (n = 48)	Physical therapy (n = 51)
Arthroscopic intervention for meniscal tear in contralateral knee	1	1
Rupture of ACL with ACL reconstruction	0	1
Arthroscopic intervention for failure of meniscal repair	1	0
Non-knee related surgery or hospital admission	4[a]	2[b]

ACL = anterior cruciate ligament
a 1 surgery for carpal tunnel syndrome, 1 laparoscopy for abdominal cyst, 1 neurosurgery for brain tumour, 1 surgery for obstructive sleep apnoea syndrome
b 1 surgery at the otorhinolaryngology department, 1 allergic reaction after intravenous contrast for contrast MRI for a femoral lesion

Post hoc analysis

The results of the post hoc as treated evaluations of the course in IKDC score are reported in Appendix 3. Four groups are reported: meniscal surgery, physical therapy, physical therapy plus delayed arthroscopic partial meniscectomy and no therapy (patients randomised to surgery who did not have surgery).

DISCUSSION

This is the first study to our knowledge comparing arthroscopic partial meniscectomy with physical therapy for traumatic meniscal tears in young patients with stable non-osteoarthritic knees. We did not find that arthroscopic partial meniscectomy was superior to physical therapy plus optional delayed arthroscopic partial meniscectomy at 24-month follow-up. Both groups showed clinically relevant improvements during the 24-month follow-up but did not achieve maximum IKDC scores at final follow-up. Fifty-nine percent of the patients in the physical therapy group did not receive a delayed arthroscopic partial meniscectomy.

Arthroscopic surgery for meniscal injuries has become the most widely performed orthopaedic surgery in the world.[1-3] This growth was based on a number of assumptions about the ability of surgery to achieve superior outcomes compared to non-surgical treatments. Over time, these have been questioned based on high quality clinical studies. These high quality studies examined the effectiveness in older patients with degenerative meniscal tears.[6, 7] This has led to a change in clinical practice guidelines. In the current guidelines a strong recommendation is made against surgery and non-surgical treatment is recommended.[9, 10] Until recently there were no clinical guidelines for traumatic meniscal injury. In 2019, the European Society for Sports Traumatology, Knee Surgery and Arthroscopy (ESSKA) published a consensus on the treatment of traumatic meniscal tears, stating that meniscus preservation should be the first choice of treatment.[12] This consensus was based on low-quality evidence due to a lack of randomised studies. Clinical trials focusing on patients with traumatic meniscal tears are sparse, and RCTs comparing arthroscopic partial meniscectomy to non-operative treatment for this specific patient group were lacking. We studied a young homogeneous population with stable non-osteoarthritic knees and a clear isolated recent traumatic meniscal tear.

This study was designed as a superiority trial, and we did not find that arthroscopic partial meniscectomy was superior to physical therapy plus optional delayed arthroscopic partial meniscectomy in the treatment of traumatic meniscal tears. At 24-month follow-up, we found a between group difference of 0.1 out of 100 points in the IKDC scores of both treatment groups, with 95% confidence interval of -7.6 to 7.7. To date no papers have been published on the MCID of the IKDC score in traumatic meniscal injuries, but new data is now available on the MCID of the IKDC score in anterior cruciate ligament ruptures (13.9) and in degenerative meniscal injuries (10.9).[27, 28] Our 95% confidence interval did not exceed both available MCIDs, neither did it exceed an effect size of 0.5 as used in the initial sample size calculation. Therefore, our study also showed that it is unlikely that arthroscopic partial meniscectomy is clinically relevant superior to physical therapy.

A strength of our study is that it is the first RCT investigating treatment of traumatic meniscal tears with a 24-month follow-up in a young study population. We had less loss to follow-up than expected. Our study has several limitations. First, preference of patients for a treatment may have induced recruitment bias, and our results may therefore not apply to those with strong treatment preference. Secondly, the primary analysis is subject to selection bias due to missing data and absence of blinding patients for the intervention. Thirdly, in the Dutch healthcare system patients with knee complaints are mainly referred to an orthopaedic surgeon within several months after the trauma. We included patients with a wide range of time from trauma to inclusion, 0 to 6 months. This may have resulted in a subgroup of patients that already followed non-operative treatment before inclusion, which may have led to a better knee function at study enrolment. Given the comparable IKDC scores at baseline, these influences were equally divided between both treatment groups. In both groups a similar number of patients reported that they had already received physical therapy before inclusion.

Although this is the first RCT in this context, our results suggest that there is a reasonable alternative to early arthroscopic partial meniscectomy as first-line treatment in patients with a traumatic meniscal tear. The challenge is predicting which patients will benefit from arthroscopic partial meniscectomy and who will improve with non-surgical treatment. Further studies should investigate whether we can already predict at an early stage who will need surgery and who will have good prognosis with physical therapy. In our study, 41% of the patients randomised to physical therapy still underwent an arthroscopic partial meniscectomy during follow-up. In studies investigating degenerative tears, 20 to 30 percent of the patients who started with physical therapy crossed-over to arthroscopic partial meniscectomy.[5, 6, 8, 29, 30] Changing the treatment paradigm for traumatic meniscal tears to a more conservative treatment may also have major impact on treatment costs and result in large health care savings.

CONCLUSION

We did not find that arthroscopic partial meniscectomy was superior to physical therapy plus optional delayed arthroscopic partial meniscectomy at 24-month follow-up in young patients with isolated traumatic meniscal tears. Fifty-nine percent of patients randomised to physical therapy did not undergo delayed arthroscopic partial meniscectomy during the follow-up period.

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Chapter 5

Cost-effectiveness of arthroscopic partial meniscectomy versus physical therapy for traumatic meniscal tears in patients aged under 45 years

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ABSTRACT

Aims

The aim of this study was to evaluate the cost-effectiveness of arthroscopic partial meniscectomy versus physical therapy plus optional delayed arthroscopic partial meniscectomy in young patients with traumatic meniscal tears.

Methods

We conducted a multicentre, open-labelled, randomized controlled trial in patients aged 18-45 years, with a recent onset, traumatic, MRI-verified, isolated meniscal tear without knee osteoarthritis. Patients were randomized to arthroscopic partial meniscectomy or standardized physical therapy with an optional delayed arthroscopic partial meniscectomy after three months of follow-up. We performed a cost-utility analysis on the randomization groups to compare both treatments over a 24-month follow-up period. Cost-utility was calculated as incremental costs per quality-adjusted life year (QALY) gained of arthroscopic partial meniscectomy compared to physical therapy. Calculations were performed from a healthcare system perspective and a societal perspective.

Results

A total of 100 patients were included. Forty-nine were randomized to arthroscopic partial meniscectomy and 51 to physical therapy. In the physical therapy group, 21 patients (41%) received delayed arthroscopic partial meniscectomy during follow-up. Over 24 months, patients in the arthroscopic partial meniscectomy group had a mean 0.005 QALYs lower quality of life (95% confidence interval -0.13 to 0.14). The cost-utility ratio was -160,000 €/QALY from the healthcare perspective and -223,372 €/QALY from the societal perspective, indicating that arthroscopic partial meniscectomy incurs additional costs without any added health benefit.

Conclusion

Arthroscopic partial meniscectomy is unlikely to be cost-effective in treating young patients with isolated traumatic meniscal tears. Arthroscopic partial meniscectomy leads to a similar quality of life but higher costs, compared to physical therapy plus optional delayed arthroscopic partial meniscectomy.

INTRODUCTION

Traumatic meniscal tears are a common knee injury in a young active population. This type of meniscal tears usually occurs during sports-related trauma.[1] Traumatic meniscal tears limit patients in their activities during daily life and sports. As a consequence, this can lead to loss of quality of life (QoL).[2] Having a meniscal tear results in a six fold increased risk of developing osteoarthritis (OA) of the knee joint, resulting in increased healthcare consumption.[3, 4] Meniscal tears also have a huge impact on a societal level, e.g. reduced work productivity and increased work absence. Yearly, approximately 30,000 meniscectomies are performed in the Netherlands, of which half are on patients aged under 45 years.[5] These young patients are often in the midst of their working life, leading to an increased socioeconomic burden.

Traumatic meniscal tears can either be treated surgically, by an arthroscopic partial meniscectomy or meniscal repair, or non-surgically, by physical therapy with exercises.[6, 7] Where patients opt for non-operative treatment with physical therapy, they may require surgery at a later time due to persistent knee symptoms. Arthroscopic meniscal surgical treatment carries some risk, though low, of serious complications, such as septic arthritis (0.135% to 0.211%), (deep) venous thromboembolism (0.413 to 0.568%) and pulmonary embolism (0.078% to 0.145%).[8, 9]

Since resources in healthcare are scarce, there is a need to investigate the cost-effectiveness of the treatment of traumatic meniscal tears.[10] A cost-effectiveness analysis can determine which treatment results in the most health gain and at what cost. So far, studies that evaluated the costs of meniscal tear treatment only analyzed patients with a degenerative meniscal tear.[11, 12] No study has investigated the cost-effectiveness of treatment of traumatic meniscal tears in young patients before. In this study we compare arthroscopic partial meniscectomy with physical therapy with respect to costs and quality of life. The aim of this study was to evaluate the cost-effectiveness of an arthroscopic partial meniscectomy versus physical therapy plus optional delayed arthroscopic partial meniscectomy in young patients with a traumatic meniscal tear, by using data of a recent randomized controlled trial (RCT) that compared both interventions.[13] In this RCT early arthroscopic partial meniscectomy was not superior to a strategy of physical therapy with optional delayed arthroscopic partial meniscectomy at 24-month follow-up.

METHODS

Study design and participants

This study is performed with data from the Study of Traumatic tears: Arthroscopic Resection vs Rehabilitation (STARR) trial, a multicentre open-labelled RCT for treatment of traumatic meniscal tears.[13] Patients were recruited between August 2014 and November 2018. We included patients aged 18-45 years with an isolated MRI-verified traumatic meniscal tear. Exclusion criteria were: a locked knee (i.e. when the patient was unable to fully extend or flex the injured knee, confirmed by clinical exam), a meniscal tear that was suitable for suture repair based on MRI findings[14], a concurrent rupture of the anterior or posterior cruciate ligament, radiographic signs of OA in the index knee (Kellgren Lawrence[15] grade 2 or higher), disabling comorbidity, or insufficient command of the Dutch or English language. Full description of the study can be found in the clinical outcome study.[13] The Erasmus MC University Medical Centre ethics committee approved the research protocol, and all patients gave written informed consent. The trial was registered at the Netherlands Trial Register with trial number NL4380 (NTR4511).

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Patient involvement

Our patient panel consisted of 3 patients with a traumatic meniscal tear. The trial set up was discussed with a panel of people with acute knee injuries before the subsidy request was submitted. In collaboration with these patients, we made our study protocol as similar as possible to our usual clinical follow-up periods and standard measurements. Since 2010 we have expanded our use of patient participation panels on a regular basis. We plan to disseminate the study results to study participants.

Interventions

Patients were randomized to either arthroscopic partial meniscectomy or physical therapy in a 1:1 ratio. Arthroscopic partial meniscectomy was performed within 6 weeks after inclusion. Postoperatively patients were treated according to routine clinical practice and the Dutch national guidelines without standard referral to physical therapy.[16] Physical therapy consisted of a standardized exercise program supervised by a physical therapist and home exercises (Appendix 1). Delayed arthroscopic partial meniscectomy was allowed in the physical therapy group after at least three months of physical therapy, in case of persistent knee complaints and in consultation with the orthopaedic surgeon.

Outcomes

Data on quality of life, healthcare costs and productivity costs were collected through patient questionnaires at baseline, 3, 6, 9, 12 and 24 months. We assessed QoL with the 3-Level EuroQol Questionnaire (EQ-5D-3L), because the EQ-5D with 5 levels was not available yet at the start of our study.[17] The EQ-5D-3L measures five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension consists of three levels: no problems, some problems and extreme problems. The outcome score of the EQ-5D-3L is between 0 and 1, with 1 as best QoL and 0 as very poor, comparable to death. For each patient the number of quality-adjusted life years (QALYs) during the 24-month follow-up (taking account of all measurement moments) was calculated as an area under the curve (maximum is 2 QALYs per person over a period of 2 years). QALYs were calculated as follows as area under the curve: QALYs year 1=[(q0 +q3)/2+(q3+q6)/2+(q6+q9)/2+(q9+q12)/2]/4. QALYs year 2=(q12+q24)/2. Total QALYS over 2 years=QALYs year 1+QALYs year 2.

Healthcare costs included costs of hospital care, non-hospital care (such as physical therapy or general practitioner visits) and medication use related to pain. Utilization of healthcare was measured with the Medical Consumption Questionnaire on the above mentioned measurement moments.[18] Healthcare costs were valued monetarily using diagnosis treatment combination tariffs, standard medication prices[19] and updated reference prices from the Dutch Costing manual for economic evaluations in healthcare.[20]

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Productivity costs included costs related to paid work (lost productivity at work (presenteeism) and absence from work (absenteeism)) and costs related to unpaid work (lost productivity or inability to perform unpaid work, such as household tasks). Productivity costs were measured with the Productivity Costs Questionnaire and valued using the often-used, valid, friction cost method that limits long-term productivity costs, as unemployment permits replacement of ill workers after an adaptation period.[21, 22]

A budget impact analysis was performed, to estimate the impact on the Dutch health care budget if the current practice of performing arthroscopic partial meniscectomy for treatment of traumatic meniscal tears would be replaced by physical therapy with optional delayed arthroscopic partial meniscectomy.

All costs were valued in euros for the year 2018. For the second year, costs and health effects were discounted: costs by 4% and QALYs by 1.5% conform the Dutch guidelines for economic evaluation in healthcare.[20]

Statistical analysis

We analyzed all patients according to their randomly assigned treatment (intention-to-treat). Over the period of 24 months, the difference in area under the curve of the QoL between groups was calculated to determine the number of QALYs gained or lost for arthroscopic partial meniscectomy compared to physical therapy.

Cost-utility was calculated as incremental costs per QALY gained of arthroscopic partial meniscectomy compared to physical therapy. Calculations were performed from a healthcare system perspective (medical costs) and a societal perspective (medical and productivity costs).

Missing values for costs and/or QoL were imputed based on linear interpolation in case the amount of missing values was less than 20%. Costs and QALYs were summed over the 24-month study period using the information of all follow-up moments.

The uncertainty for costs and health effects was assessed by means of non-parametric bootstrapping, in which 5000 observations were randomly drawn from the available study. The incremental costs and health effects for each bootstrap sample were displayed on a cost-effectiveness plane.

RESULTS

Patients

Of the 100 patients included in the study, 49 were randomized to arthroscopic partial meniscectomy and 51 to physical therapy (see Table 1). Six patients (12%) of the arthroscopic partial meniscectomy group received no surgical treatment; in 4 patients knee complaints had resolved before surgery, 1 patient withdrew from the study and 1 patient did not plan a surgery date and could not be reached. Four (8%) patients of the arthroscopic partial meniscectomy group had a meniscal repair instead of meniscectomy. Twenty-one patients (41%) of the physical therapy group underwent a delayed arthroscopic partial meniscectomy during the 24-month follow-up, because of persistent knee complaints. Final follow-up was completed for 91% of all included patients. The cost and quality of life data during follow-up had 10% missing values.

Table 1. Baseline characteristics

	Arthroscopic partial meniscectomy (n=48[a])	Physical therapy (n=51)
Age at inclusion, years	34.1 (8.6)	35.6 (7.5)
Male sex, n (%)	37 (77.1)	38 (74.5)
BMI, kg/m^2	25.5 (4.2)	26.1 (4.6)
Tegner pre-injury (0-10)	6.5 (2.2)	6.4 (2.0)
College education, no. (%)	15 (31.2)	25 (49.0)
Paid work, no. (%)	38 (79.2)	46 (90.2)
EQ-5D	0.741 (0.23)	0.733 (0.24)

Data is presented as mean with standard deviation or reported otherwise.
a Of the 49 patients randomized to arthroscopic partial meniscectomy 1 patient withdrew from the study.

Quality of life

Patients in the arthroscopic partial meniscectomy group had a total of 1.680 QALYs (standard deviation (SD) of 0.36) during the two-year study period, compared to a total of 1.685 QALYs (SD of 0.33) in the physical therapy group (between-group difference 0.005 with 95% confidence interval (CI) -0.13 to 0.14).

Figure 1 shows the quality of life pattern over time for both treatment arms. Quality of life increased substantially over time and reached the level of the general population of the same age group at the end of the second year. Differences in quality of life between the treatment arms were not clinically relevant, nor statistically significant.

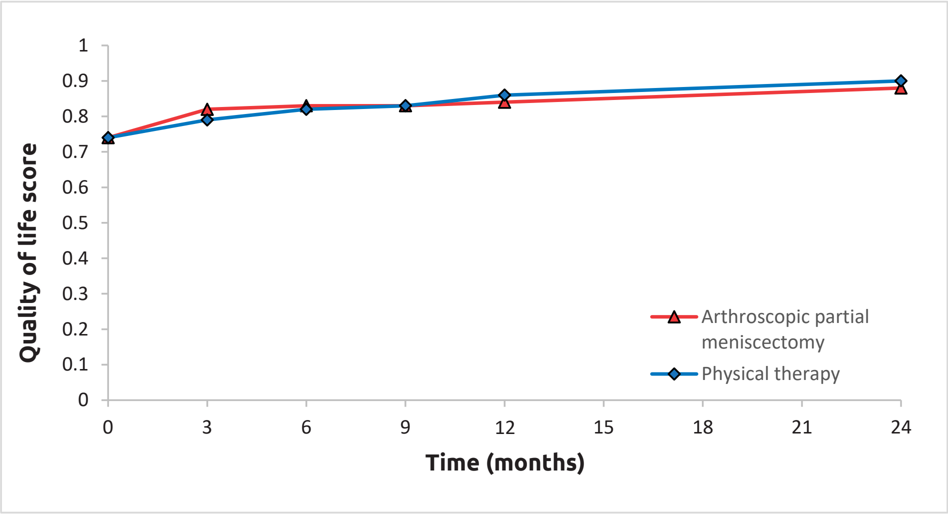

Figure 1. Average quality of life per treatment arm, per measurement moment

Costs

The healthcare costs were €3,645 in the arthroscopic partial meniscectomy group and €2,881 in the physical therapy group (Table 2). Hospital costs make up the majority of healthcare costs in both treatment arms. Within hospital costs, surgery costs dominate, especially in the arthroscopy arm, but also in the physical therapy arm, since 41% of the patients randomized to physical therapy eventually underwent surgery during the follow-up period (n=21).

Productivity costs were €6,037 in the arthroscopic partial meniscectomy group and €5,778 in the physical therapy group (Table 2). Most productivity costs were related to paid work. Absence from work and lost productivity at work were not frequent, leading to a large variance in productivity costs between patients, which is often seen in studies of musculoskeletal disorders.[23-25]

Table 2. Average costs and QALYs per patient per treatment arm in Euros

	Arthroscopic partial meniscectomy (n=48)	Physical therapy (n=51)
HEALTH CARE		
Hospital costs (SD)	3,307 (1,335)	2,165 (1,724)
Non-hospital costs		
Social worker	3	5
general practitioner	23	40
occupational medicine	17	13
physical therapist and homoeopathist	289	642
Sum non-hospital	332	701
Pain medication	6	16
1. Total costs from healthcare perspective (SD)	**3,645 (1,404)**	**2,881 (2,369)**
SOCIETAL		
Absence paid work	3,100	2,290
Presenteeism paid work	2,498	2,839
Lost unpaid work	438	649
2. Productivity costs total (SD)	**6,037 (9,397)**	**5,778 (10,345)**
Total costs from societal perspective (1+2)	**9,681**	**8,659**
Number of QALYs over 2 years (SD)	**1.680 (0.36)**	**1.685 (0.33)**

Data is presented as costs in Euros (€) with standard deviation (SD).

Cost-utility

The results of the cost-utility analysis for both treatment strategies are presented in Table 3. Using the healthcare and societal perspectives it turns out that performing arthroscopic partial meniscectomy instead of physical therapy for patients with traumatic meniscal tears incurs additional costs (€764 to €1,022) and leads to decrease in QALYs of 0.005. The Incremental Cost Effectiveness Ratios shown in Table 3 are negative and illustrate that arthroscopic partial meniscectomy is inferior to physical therapy for these patients. Alternatively phrased, physical therapy dominates arthroscopic partial meniscectomy as it is less expensive and at least as effective in terms of QALYs.

Table 3. Cost-utility results of arthroscopic partial meniscectomy versus physical therapy

	Healthcare system perspective	**Societal perspective**
Incremental cost (in €)	+764	+1,022
Incremental QALY's	-0.005	-0.005
Incremental cost per QALY (ICER in €)*	-160,000	-223,372

ICER = incremental cost-effectiveness ratio of arthroscopic partial meniscectomy versus physical therapy
QALY = quality-adjusted life year
* In this case, these negative ICERS mean that performing an arthroscopic partial meniscectomy instead of physical therapy for these patients incurs additional costs, whereas no health benefit is produced.

The uncertainty analysis shows that using the healthcare perspective, arthroscopic partial meniscectomy led to a lower quality of life in 53% of the bootstrap replications and this treatment was more expensive in 95% of the replications (Figure 2). Applying the societal perspective, arthroscopic partial meniscectomy led to a lower quality of life in 50% of the bootstrap replications and higher costs in 74% of the replications (Figure 3).

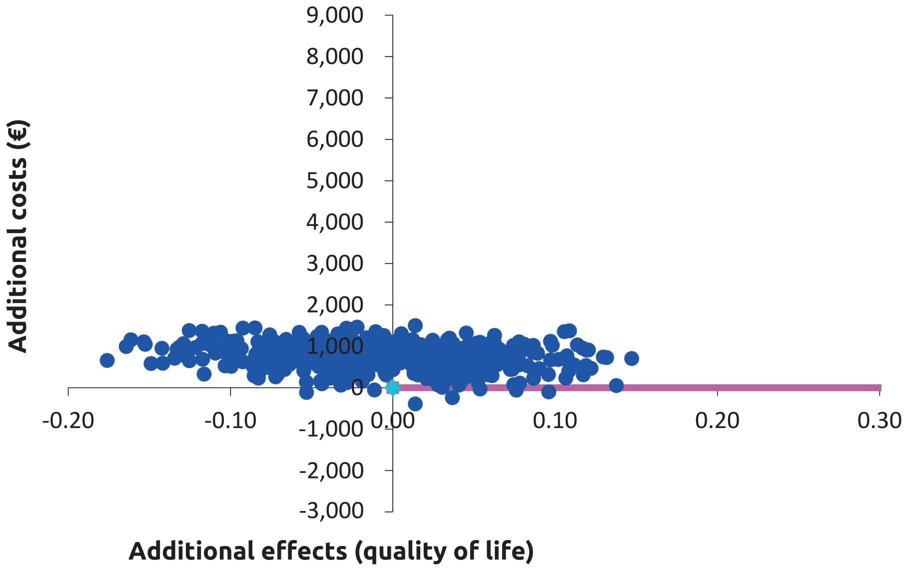

Figure 2. Uncertainty analysis (health care perspective)

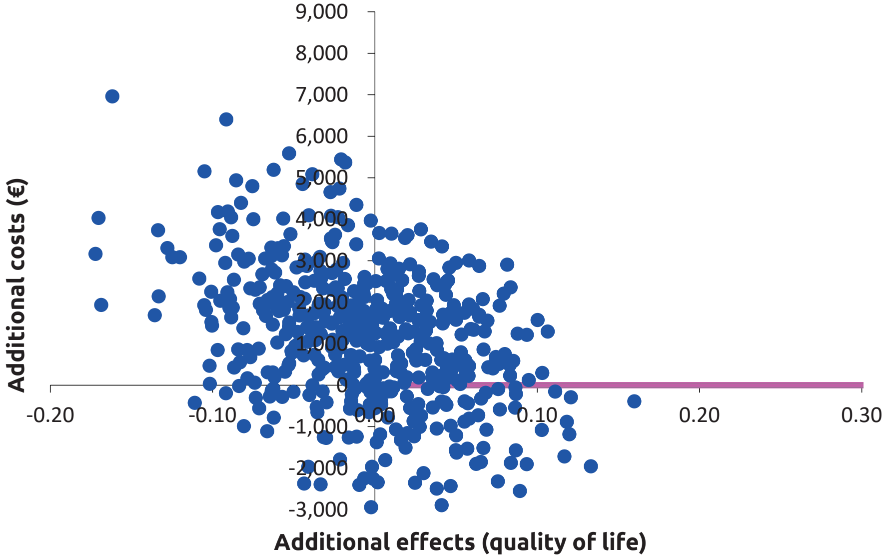

Figure 3. Uncertainty analysis (societal perspective)

5

Budget impact analysis

About 30,000 arthroscopic partial meniscectomies are performed annually in the Netherlands.[5] Half of these are performed under age 45, the target group of our study.[5] A more conservative treatment guideline could result in 40% fewer arthroscopic partial meniscectomies for this age group, resulting in 6,000 fewer surgeries per year. According to our study, these patients will get more physical therapy, about €340 per patient. The estimated annual budget impact of a more conservative guideline will be 6000 * 3200 = €19.2 million savings in hospital costs and 6000 * 340 = €2 million extra costs for physical therapy. On balance, about €17 million could be saved annually in the Netherlands without any expected health loss in terms of QALYs.

DISCUSSION

Our cost-effectiveness analysis of arthroscopic partial meniscectomy compared to physical therapy plus optional delayed arthroscopic partial meniscectomy in young patients with a traumatic meniscal tear showed that arthroscopic partial meniscectomy resulted in similar QoL during 24 months and led to higher costs. This resulted in a cost-utility ratio of €-160,000/QALY from the healthcare perspective and €-223,372/QALY from the societal perspective. These negative cost-utility ratios indicate that performing an arthroscopic partial meniscectomy instead of offering physical therapy plus optional delayed arthroscopic partial meniscectomy for these patients incurs additional costs, whereas no health benefit is produced. Our budget impact analysis showed that in the Netherlands, about €17 million could be saved annually if patients with traumatic meniscal tears are initially treated with physical therapy instead of arthroscopic partial meniscectomy. Study interpretation should consider that 41% of the patients who started with physical therapy underwent delayed arthroscopic partial meniscectomy during follow-up. Based on this study, arthroscopic partial meniscectomy is unlikely to be cost-effective compared to physical therapy plus optional delayed arthroscopic partial meniscectomy in the treatment of traumatic meniscal tears in patients under 45 years.

After 24 months, patients reached a QoL level of 0.88 in the arthroscopic partial meniscectomy group and 0.90 in the physical therapy group, comparable to the QoL in healthy people of the same age.[26] During the entire study period, we found a 0.005 QALYs (95% CI -0.13 to 0.14) lower QoL in the arthroscopic partial meniscectomy group compared to the physical therapy group. In the EQ-5D-3L questionnaire 0.07-0.08 QALYs is considered a minimally important difference in QoL.[27, 28] We can state that patients with a traumatic meniscal tear, treated with either arthroscopic partial meniscectomy or physical therapy, have no relevant nor statistically significant difference in QoL during 24-month follow-up. This result is in line with the clinical outcomes in our previously reported results (the STARR trial), such as the International Knee Documentation Score, which did not differ between treatment groups after 24-month follow-up.[13] From a clinical and health economics perspective, our results suggest that physical therapy is a reasonable alternative to early arthroscopic partial meniscectomy as first-line treatment in young patients with a traumatic meniscal tear.

The STARR trial is the first RCT comparing arthroscopic partial meniscectomy with physical therapy plus optional delayed arthroscopic partial meniscectomy in young patients with traumatic meniscal tears. Cost-utility analyses of these treatments in young patients with traumatic meniscal tears have not been done before. However, there are some cost-effectiveness studies on treating older patients with degenerative meniscal tears.[11, 12] These studies showed that arthroscopic partial meniscectomy is not cost-effective as a first-line treatment in patients with degenerative meniscal tears. In this study we found comparable results, indicating that arthroscopic partial meniscectomy is unlikely to be cost-effective in treating patients under 45 years with traumatic meniscal tears.

Interpretation of this study should consider that 41% of the patients who started with physical therapy underwent arthroscopic partial meniscectomy during follow-up. In this study we only analyzed the as randomized treatment groups, which may not fully represent potential differences between patients who followed physical therapy only and those who underwent delayed arthroscopic partial meniscectomy after an initial period of physical therapy. Further studies should indicate whether QoL of patients who underwent delayed arthroscopic partial meniscectomy is comparable to patients who required physical therapy only. Costs for the physical therapy group will probably decrease and treatment quality could increase if we can predict which patients will need an arthroscopic partial meniscectomy, by reducing patients who receive both physical therapy and surgery.

Our study did not include the risk for OA for both treatments, since a follow-up period of 24 months is relatively short to investigate this. It is known that patients with meniscal tears have an increased risk for OA.[3] On the long-term, differences between both treatment groups in the development of OA may influence healthcare costs, thereby influencing the cost-effectiveness.

Our study has several strengths. First, this is the first RCT investigating cost-effectiveness of arthroscopic partial meniscectomy in patients with a traumatic meniscal tear. Second, our trial's follow-up period of 24 months is relatively long for an empirical cost-utility analysis without long-term modelling. Third, we included the societal perspective in our analyses, like productivity loss and work absence, which other cost-effectiveness studies often do not include.

A limitation of our study is that we studied a relatively small study population of 100 patients, compared to other cost-effectiveness studies. We also used the EQ5D-3L questionnaire, a previous version of the currently used EQ5D-5L questionnaire, since the EQ5D-5L was not validated for economic evaluations at the start of our study.[29] We valued all costs in euros for the year 2018. Updating the costs to 2021 would include multiplying all costs by factor 1.068 based on Statistics Netherlands, including costs of lost or gained QALYs.

CONCLUSION

In young patients with isolated traumatic meniscal tears, arthroscopic partial meniscectomy leads to a similar QoL but higher costs compared to physical therapy plus optional delayed arthroscopic partial meniscectomy. Study interpretation should consider that 41% of the patients who started with physical therapy were indicated for and underwent arthroscopic partial meniscectomy during follow-up. Arthroscopic partial meniscectomy is not likely to be the most cost-effective primary treatment of young patients with traumatic meniscal tears.

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Chapter 6

Concurrent abnormalities on MR imaging in a young study population with isolated traumatic meniscal tears

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ABSTRACT

Objective

To identify posttraumatic and osteoarthritis related lesions on MRI in young patients with isolated traumatic meniscal tears and without radiographic osteoarthritis compared to healthy control knees.

Design

We included patients aged 18 to 45 years with traumatic meniscal tears without radiographic osteoarthritis and healthy controls aged 18 to 40 years. We analyzed baseline MRIs of patients and controls with the MRI Osteoarthritis Knee Score. We reported bone marrow lesions (BMLs), cartilage defects and osteophytes for patients and controls. In patients, the overlap between meniscal tear location and BMLs was presented.

Results

We included 99 patients with traumatic meniscal tears and 50 healthy controls. At baseline 72% of the patients (n=72) had one or more BMLs grade 1 or higher, compared to 44% of the controls (n=22). Grade 2 and 3 BMLs were present in 26% of the patients (n=26), compared to 2% of the controls (n=1). In patients, 35% (n=35) had one or more cartilage defects grade 1 or higher, compared to 2% of controls (n=1). Osteophytes grade 2 or higher were present in 21% of the patients (n=21) and 18% of the controls (n=9). Half of the patients had a BML in the same compartment as their meniscal tear.

Conclusions

In this first study that investigated MRI findings in patients with isolated traumatic tears, we found more severe BMLs and cartilage defects in patients compared to controls. Only half of the patients had a BML in the same compartment of the knee as the meniscal tear.

INTRODUCTION

Isolated traumatic meniscal tears typically occur by definition in young patients and they usually are the result of a sports-related trauma.[1, 2] It is assumed that these young knees were healthy before the trauma and without any posttraumatic or osteoarthritis (OA) related abnormalities other than the meniscal tear. A traumatic meniscal tear increases the long-term risk of OA, but the direct impact of the trauma on the knee joint is unknown.[3] MRI can detect different OA-related features in the knee joint, such as bone marrow edema, cartilage defects and osteophytes.[4] Bone marrow edema can occur at the location of a direct trauma or may show typical patterns matching various indirect trauma mechanisms.[4, 5] Cartilage damage can also be caused by acute trauma of the knee joint. Both bone marrow changes and cartilage defects can also be present in the osteoarthritic knee joint. OA of the knee joint is also characterized by osteophytes.[6]

In other common knee injuries, like anterior cruciate ligament (ACL) ruptures, concurrent MRI features related to OA have been described in the literature, including the prevalence of cartilage defects and bone marrow edema patterns.[7-9] Asymptomatic knees may also have OA-related features on MRI.[10] So far, no studies have investigated posttraumatic or OA-related MRI findings in patients with isolated traumatic meniscal tears.

In a recent randomized controlled trial (RCT), we studied two treatment strategies in young patients with traumatic meniscal tears without radiographic OA.[11] All patients of this unique homogeneous study population had an MRI at baseline. Although all patients had no signs of knee OA on radiographs, MRI can detect more subtle abnormalities.[4] Our study aimed to identify posttraumatic and OA-related lesions on MRI in young patients with isolated traumatic meniscal tears and without radiographic OA compared to healthy control knees.

METHODS

Study design

We used the baseline data of patients with a traumatic meniscal tear who participated in the STARR trial and data of healthy controls from the Triple P study.[11, 12]

The STARR study was an open-labelled, multicenter, parallel RCT named Study of Traumatic meniscal tears: Arthroscopic Resection vs Rehabilitation trial. Patients were recruited between August 2014 and November 2018 in 8 hospitals (1 university hospital and 7 non-university hospitals) in the Netherlands. The Erasmus University Medical Centre ethics committee approved the research protocol, and all patients gave written informed consent. The trial was registered in the Netherlands Trial Register (NL4380, NTR4511 https://trialsearch.who.int/Trial2.aspx?TrialID=NTR4511) prior to the inclusion of the first subject. Clinical outcomes have been published before.[11]

The Triple P study was conducted between January 2013 and September 2014 in patients with patellofemoral pain and healthy controls.[12] This study was a cross-sectional case-control study performed in 1 university hospital in the Netherlands. All patients gave written informed consent and the study was approved by an institutional review board (Erasmus University Medical Centre ethics committee).

Study population

Patients with symptomatic traumatic meniscal tears from the STARR study were recruited from outpatient clinics of the participating hospitals. Patients aged 18 to 45 years with a clinical suspicion for meniscal lesion, a knee trauma in the previous six months and a grade 3 meniscal tear on MRI were eligible for study participation if the MRI images were available for analysis. A grade 3 meniscal tear is defined by high-intensity signal changes on MRI that reach the articular surface of the meniscus and therefore is considered a full tear.[2] Exclusion criteria were: a locked knee (i.e., when the patient was unable to fully extend or flex the injured knee), a meniscal tear that was suitable for suture repair based on MRI findings[13], a concurrent rupture of the anterior or posterior cruciate ligament, radiographic signs of OA in the index knee (Kellgren Lawrence[14] grade 2 or higher), disabling comorbidity, or insufficient command of the Dutch or English language. Eligible patients received oral and standardized written trial information.

Subjects aged 18 to 40 years with no knee complaints from the Triple P study were eligible as healthy controls. The subjects were recruited from Triple P study patients' sports team members, friends, or the university (employees and students). Exclusion criteria for controls were: patellofemoral pain at present or in the past, history of traumatic injury, or surgery of either knee.[12]

MRI evaluation

Patients had an MRI of the injured knee at baseline and all controls had an MRI of one randomly selected knee. MRIs were made on MRI scanners with a magnetic field strength of 1.5 or 3.0 Tesla. The scanning protocol and MRI scanner were identical for all controls and part of the patients (included in the Erasmus Medical Centre, n=21) and comparable for the other patients. We used the following MRI pulse sequences, which were harmonized across centers: sagittal, axial and coronal proton density turbo spin echo (TSE) sequence (slice thickness 3 mm); sagittal and axial T2-weighted TSE sequence with fat saturation (slice thickness 3 mm).

We evaluated all MRI scans using the MRI Osteoarthritis Knee Score (MOAKS).[15] The MOAKS is a semi-quantitative scoring method for knee OA features. Each feature of the MOAKS is scored in predefined sub-regions of the knee joint. The features that were used in the current study are bone marrow lesions (BMLs), cartilage defects and osteophytes. In the MOAKS BMLs were scored according to the size of the BML with respect to the sub-region it is located in. When the BML size was up to 33% of the sub-region, it was graded grade 1. BML sizes 33% to 66% were scored as grade 2. BMLs larger than 66% of the sub-region were scored grade 3. Cartilage defects are defined as loss of cartilage thickness as a percentage of the surface of a sub-region, where loss of less than 10% is scored as grade 1, loss of 10% to 75% as grade 2 and loss of more than 75% as grade 3. Osteophytes were graded as none (grade 0), small (grade 1), medium (grade 2) and large (grade 3). We scored meniscal tears as medial meniscal tear, lateral meniscal tear or both medial and lateral meniscal tear.

To implement the MOAKS adequately, all readers of the STARR study and Triple P study underwent an extensive training program supervised by an experienced musculoskeletal radiologist (15 years of experience).[16] In patients with traumatic meniscal tears, two extensively trained researchers evaluated all MRI scans using the MOAKS. All findings were discussed with the experienced musculoskeletal radiologist, together they reached consensus on all MRIs. In healthy controls, all MRI scans were scored by a trained researcher in radiology using the MOAKS. Subsequently, all findings were discussed with the experienced musculoskeletal radiologist, who made the final determination.

Outcome measures

When analyzing the MRI scores we combined sub-regions for both patients and controls.[16] We defined patellofemoral as a combination of the sub-regions patella medial, patella lateral, femur trochlea medial and femur trochlea lateral. Tibiofemoral medial was defined as a combination of the sub-regions femur central medial, femur posterior medial, tibia anterior medial, tibia central medial and tibia posterior medial. Tibiofemoral lateral was defined as a combination of the sub-regions femur central lateral, femur posterior lateral, tibia anterior lateral, tibia central lateral and tibia posterior lateral.

Data analysis

We used descriptive statistics to present the presence of BMLs, cartilage defects and osteophytes for the complete knee joint and each sub-region, for patients and controls. We reported all grades for BMLs and cartilage defects, ranging from 1 to 3. We reported osteophytes grade 2 and 3 since osteophytes grade 1 were present in all knees and are common in healthy knees as well, especially in young patients.[17] In patients, the overlap between meniscal tear location and BMLs was presented in Venn diagrams. Similarly, Venn diagrams were made of the overlap between meniscal tear location and cartilage defects. Since both studies were not powered for the current research question, we only performed descriptive statistical analysis.

RESULTS

Study population

A total of 100 patients were included in the STARR trial of which 99 were included in the current study, since one patient had a computed tomography arthrogram due to incompatibility for MRI at baseline. A total of 70 healthy controls were included in the Triple P study, of which 50 were aged between 18 and 40 years and were included in the current study. Characteristics of patients and controls are presented in Table 1. Controls were younger than patients.

Table 1. Study population characteristics

	Patients with a traumatic meniscal tear (n = 99)	Controls (n = 50)
Age at MRI, years	35.2 (8.1)	25.9 (4.4)
Male sex, n (%)	75 (76)	24 (48)
BMI (kg/m²)	25.8 (4.4)	23.2 (2.8)
Tegner pre-injury[a]	6.4 (2.1)	6.4 (1.9)
Time between trauma and MRI, days	85.7 (64.1)	
Meniscus injured during, n (%)		
sport	53 (54)	
daily activities	16 (16)	
work	18 (18)	
other	10 (10)	
Meniscal tear baseline MRI, n (%)		
medial meniscus	66 (67)	0 (0)
lateral meniscus	29 (30)	0 (0)
medial + lateral meniscus	4 (4)	0 (0)

Data is presented as mean with standard deviation in brackets unless otherwise reported. Some values of patient group are known for 98 patients instead of 99.
a The Tegner scores ranges from 0 to 10, with higher scores indicating a higher activity level.

MRI features

The prevalence of BMLs, cartilage defects and osteophytes per sub-region are presented in Table 2. At baseline 72% of the patients (n=72) had one or more BMLs grade 1 or higher, compared to 44% of the controls (n=22). Grade 2 and 3 BMLs were present in 26% of the patients (n=26), compared to 2% of the controls (n=1). In patients, BMLs were located both in the patellofemoral and tibiofemoral regions, while in controls BMLs were mainly located in the patellofemoral region. In patients, 35% (n=35) had one or more cartilage defects grade 1 or higher, compared to 2% of controls (n=1). Osteophytes grade 2 or higher were present in 21% of the patients (n=21) and 18% of the controls (n=9).

Table 2. BMLs, cartilage defects and osteophytes at baseline

	BML		Cartilage defect		Osteophyte	
	Patients (n=99)	Controls (n=50)	Patients (n=99)	Controls (n=50)	Patients (n=99)	Controls (n=50)
Total, n (%)	71 (72)	22 (44)	35 (35)	1 (2)	21 (21)	9 (18)
grade 1*	45 (46)	21 (42)	13 (13)	0 (0)	-	-
grade 2**	20 (20)	1 (2)	21 (21)	1 (2)	21 (21)	8 (16)
grade 3***	6 (6)	0 (0)	1 (1)	0 (0)	0 (0)	1 (2)
Patellofemoral, n (%)	20 (20)	21 (42)	22 (22)	1 (2)	1 (1)	1 (2)
grade 1*	13 (13)	21 (42)	9 (9)	0 (0)	-	-
grade 2**	7 (7)	0 (0)	12 (12)	1 (2)	1 (1)	0 (0)
grade 3***	0	0 (0)	1 (1)	0 (0)	0 (0)	1 (2)
Tibiofemoral medial, n (%)	48 (48)	5 (10)	6 (6)	0 (0)	16 (16)	5 (10)
grade 1*	33 (33)	4 (8)	1 (1)	0 (0)	-	-
grade 2**	11 (11)	1 (2)	5 (5)	0 (0)	16 (16)	5 (10)
grade 3***	4 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Tibiofemoral lateral, n (%)	25 (25)	3 (6)	15 (15)	0 (0)	5 (5)	3 (6)
grade 1*	17 (17)	2 (4)	9 (9)	0 (0)	-	-
grade 2**	5 (5)	1 (2)	6 (6)	0 (0)	5 (5)	3 (6)
grade 3***	3 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Number of bone marrow lesions, cartilage defects and osteophytes in the study population (n = 100) and controls (n = 50).
* worst grade present is grade 1
** worst grade present is grade 2
*** worst grade present is grade 3
BMLs = bone marrow lesions
Grade 0: none
Grade 1: <33% of sub regional volume
Grade 2: 33-66% of sub regional volume
Grade 3: >66% of sub regional volume
Cartilage defects
Grade 0: none
Grade 1: <10% of region of cartilage surface area
Grade 2: 10-75% of region of cartilage surface area
Grade 3: >75% of region of cartilage surface area
Osteophytes
Grade 0: none
Grade 1: small
Grade 2: medium
Grade 3: large

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Meniscal tear, BMLs and cartilage defects location in patients

The overlap of meniscal tear location and BMLs is presented in Figure 1. Half of the patients had a BML in the same compartment as their meniscal tear. Of patients with a medial meniscal tear, 17% (n=11) had a BML in the lateral compartment, of which six patients (55%) also had a BML in the medial compartment. Of patients with a lateral meniscal tear, 34% (n=10) had a BML in the medial compartment, of which six patients (60%) also had a BML in the lateral compartment. The overlap of meniscal tear location and cartilage defects is presented in Figure 2. Of the patients with a medial meniscal tear, 5% (n=3) had a grade 2 cartilage defect in the tibiofemoral medial sub-region. Of the patients with a lateral meniscal tear, 10% (n=3) had a grade 2 cartilage defect in the tibiofemoral lateral sub-region.

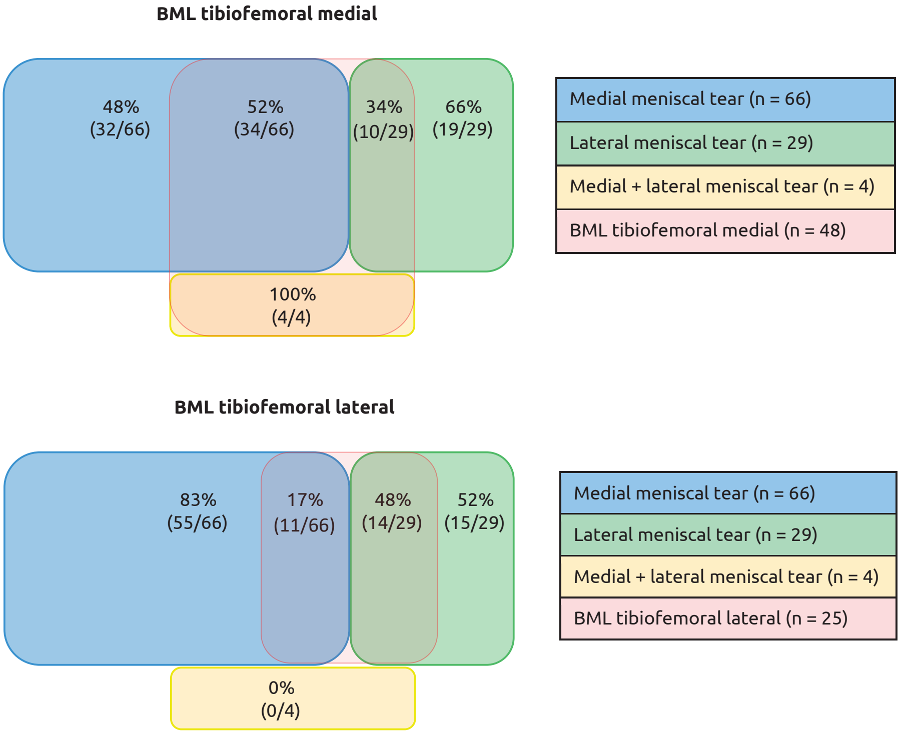

Figure 1. Overlap between meniscal tear location and BMLs
BML = bone marrow lesion
Bone marrow lesion present: grade 1 or higher

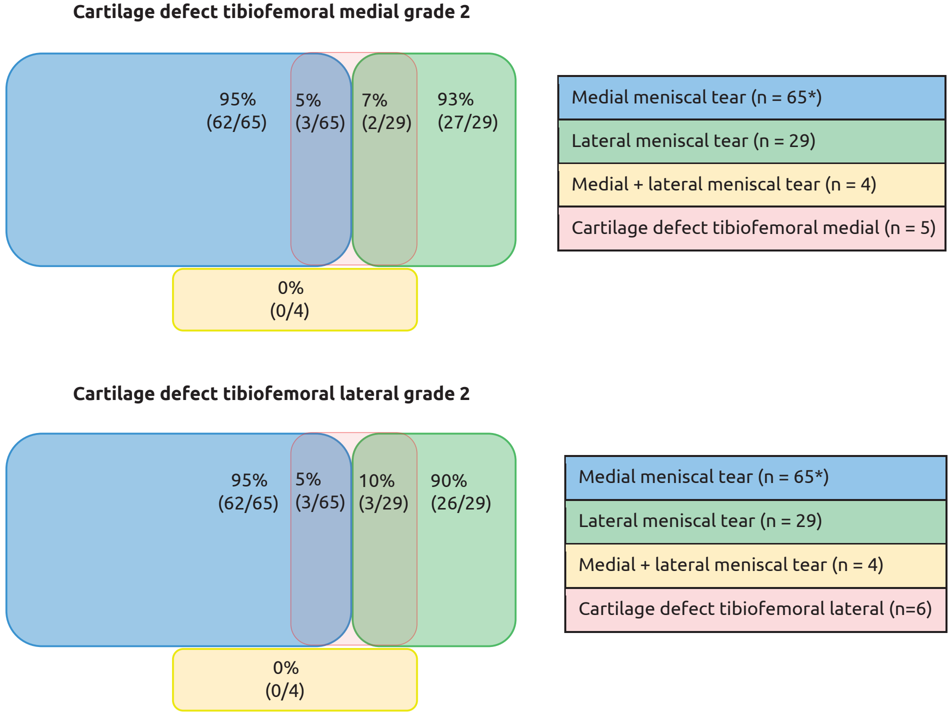

Figure 2. Overlap between meniscal tear location and cartilage defects grade 2
*1 missing in 'medial meniscal tear' because cartilage could not be graded

6

DISCUSSION

In this case-control study comparing MRI findings in patients with isolated traumatic meniscal tears without radiographic OA to healthy controls, we found more than ten times as much severe BMLs and cartilage defects in patients compared to controls. Patients had more grade 2 and 3 BMLs in the knee joint compared to controls (26% vs. 2%), while the percentage of small BMLs (grade 1) was comparable in patients and controls. Cartilage defects were mainly present in patients, 35% of the patients had a cartilage defect, compared to 2% of the controls. The prevalence of osteophytes in both groups was similar, namely 21% in patients and 18% in controls. Half of the patients had a BML in the same knee compartment as the meniscal tear.

We found large differences in the occurrence of BMLs and cartilage defects between patients and controls. To our knowledge, no previous study has described OA-related features on MRI in knee joints of young patients with isolated traumatic meniscal tears. Grade 1 BMLs were comparable between patients and controls (46 vs. 42%), but the location of BMLs was different in patients (patellofemoral and tibiofemoral) compared to controls (mainly patellofemoral). The clinical relevance of grade 1 BMLs is uncertain. More severe, clinically relevant grade 2 and 3 BMLs were more often present in patients (26 vs. 2%). Compared to other studies with MRI data from controls with asymptomatic knees, our control subjects had relatively many BMLs (44%). It is known that persons without knee complaints and presumed 'healthy' knees have structural OA-related features on MRI of the knee joint.[18, 19] A systematic review reported that the prevalence of BMLs in asymptomatic knees is between 12 to 24%, with higher percentages in athletes playing weight-bearing sports.[10] The higher prevalence of BMLs in our controls is probably due to the high activity level of our controls. Controls were recruited from the social environment of patients with patellofemoral pain, for example in the same sports team. Consequently, controls were on a similar activity level as patients with patellofemoral pain. This may have influenced the number of BMLs and may explain why controls in our study have relatively many BMLs compared to the literature on healthy knees. Also, a higher physical activity level is associated with a higher incidence of BMLs.[10, 20-22] Controls had relatively many BMLs in the patellofemoral compartment of the knee. In a recent study on MRI findings in asymptomatic knees, abnormalities were mainly located in the patellofemoral joint, comparable to our controls.[23] Cartilage defects were almost exclusively present in patients. In a systematic review, the average number of cartilage lesions in asymptomatic knees was 11% under 40 years and 43% over 40 years.[10] In our control group, the prevalence of cartilage lesions was only 2% (n=1), possibly due to the low age of our control population and the fact that they did not have a history of knee trauma. We found no clear trends for osteophytes. The percentages of osteophytes in patients and controls were comparable (21 vs 18%). We excluded grade 1 osteophytes because of their uncertain clinical relevance.[17] It is also not entirely known what having grade 2 or 3 osteophytes means for young patients and if they are associated with knee joint degeneration.[17] So where there was a clear trend in more severe BMLs and cartilage defects in patients, the clinical relevance of osteophytes in both patients and controls is not completely known.

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Half of the patients had a BML in the same compartment as the meniscal tear. This observation would fit with a minor trauma without any ligamentous injury. More severe traumas, such as traumas causing ACL ruptures, are likely to result in more BMLs because of a higher impact on the knee joint.[5, 9, 24] Assuming that a meniscal injury occurs with compression and rotation of the affected meniscus, one would expect this compression to create a BML located at the same side of the knee as the meniscal tear. Since in our patients the location of the meniscal tear and BML did correspond in about 50% of the patients, the question arises whether this is because of the low impact of the trauma or whether the origin of these BMLs is degenerative instead of genuinely traumatic. Another option may be that patients changed their load pattern of the knee by sparing the affected joint compartment.

A strength of our study is that patients belonged to a unique, homogenous, and relatively large study population with a specific symptomatic diagnosis, a recent traumatic meniscal tear in otherwise healthy knees. Therefore this study provides a representative description of MRI findings in patients with traumatic meniscal tears without radiographic OA.

A limitation of our study is that the controls are not similar to our patients since they were younger. This could have introduced some bias, which may have influenced the number of BMLs, cartilage lesions and osteophytes. With increasing age the risk of OA increases, with corresponding degenerative changes in the knee joint.[25] This age difference complicates the interpretation of relatively more BMLs and cartilage lesions in patients compared to controls. These changes in patients could be either degenerative or traumatic, but whether a bone marrow change or cartilage defect is related to the trauma or OA cannot be distinguished on MRI.[26] Therefore, we cannot state that the changes in patients can be completely contributed to the trauma that caused the meniscal injury, since age also may have influenced the number of MRI findings.

CONCLUSION

In this first study that investigated MRI findings in patients with isolated traumatic tears, we found more severe additional BMLs and cartilage defects in patients compared to controls. Only half of the patients had a BML in the same compartment of the knee as the meniscal tear.

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Chapter 7

Degenerative changes in the knee 2 years after traumatic meniscal injury: comparison of arthroscopic partial meniscectomy with physical therapy

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ABSTRACT

Objective

To assess the presence of early degenerative changes on Magnetic Resonance Imaging (MRI) 24 months after a traumatic meniscal tear and to compare these changes in patients treated with arthroscopic partial meniscectomy or physical therapy plus optional delayed arthroscopic partial meniscectomy.

Design

We included patients aged 18-45 years with a recent onset, traumatic, MRI verified, isolated meniscal tear without radiographic osteoarthritis (OA). Patients were randomized to arthroscopic partial meniscectomy or standardized physical therapy with optional delayed arthroscopic partial meniscectomy. MRIs at baseline and 24 months were scored using the MRI Osteoarthritis Knee Score. The outcome was the progression of bone marrow lesions (BMLs), cartilage defects and osteophytes after 24 months.

Results

At 24 months MRI was available for 40 patients randomized to arthroscopic partial meniscectomy and 41 patients randomized to physical therapy. At 24 months 30% (n=12) of the patients randomized to arthroscopic partial meniscectomy showed BML progression, compared to 22% (n=9) of the patients randomized to physical therapy. Progression of cartilage defects was present in 40% (n=16) of the arthroscopic partial meniscectomy group, compared to 22% (n=9) of the physical therapy group. Of the patients who had no cartilage defect at baseline, 33% of the arthroscopic partial meniscectomy group had a new cartilage defect at follow-up compared to 14% of the physical therapy group. Osteophyte progression was present in 18% (n=7) of the arthroscopic partial meniscectomy group and 15% (n=6) of the physical therapy group.

Conclusions

We found more progression of BMLs and cartilage defects with arthroscopic partial meniscectomy compared to physical therapy with optional delayed arthroscopic partial meniscectomy at 24-month follow-up in young patients with isolated traumatic meniscal tears without radiographic OA.

INTRODUCTION

Traumatic meniscal tears are common sports injuries typically occurring in a young active population. Meniscal tears often lead to pain and limit patients in their daily activities. One of the challenges in treating young patients with traumatic meniscal tears is minimizing the risk for posttraumatic osteoarthritis (OA). Patients who sustain a meniscal tear have a six fold increased risk for OA of the knee joint.[1, 2] Both surgical treatment options for a traumatic meniscal tear, arthroscopic partial meniscectomy and meniscal repair, increase the risk for knee OA.[3] Meniscal repair of traumatic meniscal tears may reduce the risk for OA compared to arthroscopic partial meniscectomy by 40 percent, but still is associated with a higher risk compared to the general population.[4]

Currently, young patients with acute meniscal tears in previously healthy knees are usually offered surgery.[5, 6] Around 200,000 arthroscopic partial meniscectomies are performed annually in patients under 45 years in the United States.[7, 8] However, a recent randomized controlled trial (RCT) showed that in young patients with isolated traumatic meniscal tears, arthroscopic partial meniscectomy is not superior to physical therapy plus optional delayed arthroscopic partial meniscectomy with regard to clinical outcomes at 24-month follow-up.[9] Clinical outcomes include possible persistent complaints after 24 months that may be caused by early OA. This raises the question whether these two treatment options lead to a difference in early degenerative changes after 24-month follow-up and whether we should take this into account when choosing the optimal treatment for traumatic meniscal tears. Magnetic resonance imaging (MRI) is an important imaging tool for OA research, since it can visualize all structures of the knee joint involved in OA.[10] MRI can also visualize other changes in the knee joint compared to radiographs, such as bone marrow edema and cartilage defects.[10] The aim of this study is to assess the presence of early degenerative changes on MRI 24 months after a traumatic meniscal tear and to compare these changes in patients treated with arthroscopic partial meniscectomy or physical therapy plus optional delayed arthroscopic partial meniscectomy.

METHODS

Study design

The Study of Traumatic meniscal tears: Arthroscopic Resection vs Rehabilitation (STARR) trial was an open-labelled, multicenter, parallel RCT. [9] The present study is a secondary analysis of the STARR trial. Patients were recruited between August 2014 and November 2018 in 8 hospitals (1 university hospital and 7 non-university hospitals) in the Netherlands. The Erasmus University Medical Center ethics committee approved the research protocol, and all patients gave written informed consent. The trial was registered in the Dutch Trial Register prior to the inclusion of the first subject (NTR4511, https://trialsearch.who.int/).

Patients

Patients were recruited from outpatient clinics of the participating hospitals. Patients aged 18 to 45 years with a knee trauma in the previous 6 months, clinical suspicion for meniscal lesion, and a grade 3 meniscal tear on MRI were eligible for study participation. A grade 3 meniscal tear is defined by high intensity signal changes on MRI that reach the articular surface of the meniscus and therefore is considered to be a full tear.[11] Exclusion criteria were: a locked knee (i.e. when the patient was unable to fully extend or flex the injured knee), a meniscal tear that was suitable for suture repair based on MRI findings[12], a concurrent rupture of the anterior or posterior cruciate ligament, radiographic signs of OA in the index knee (Kellgren Lawrence[13] grade 2 or higher), disabling comorbidity, or insufficient command of the Dutch or English language. Eligible patients received oral and standardized written information about the trial.

Interventions

Patients were randomized to arthroscopic partial meniscectomy or physical therapy in a 1:1 ratio. Arthroscopic partial meniscectomy was performed within 6 weeks after inclusion. Postoperatively, patients were treated according to routine clinical practice and the Dutch national guidelines, without standard referral to physical therapy.[14] Physical therapy consisted of a standardized exercise program supervised by a physical therapist and home exercises. Delayed arthroscopic partial meniscectomy was allowed in the physical therapy group after at least 3 months of physical therapy.

MRI evaluation

Patients underwent an MRI of the injured knee at baseline and after 24-month follow-up. MRIs were acquired on whole-body MRI scanners with a magnetic field strength of 1.5 or 3.0 Tesla. The scanning protocol and MRI scanner were identical for part of the patients (patients included in the Erasmus MC, Rotterdam, n=21) and comparable for the other patients. We used the following MRI pulse sequences which were harmonized across centers: sagittal, axial and coronal proton density turbo spin echo (TSE) sequence (slice thickness 3 mm); sagittal and axial T2-weighted TSE sequence with fat saturation (slice thickness 3 mm).

We evaluated all MRI scans using the MRI Osteoarthritis Knee Score (MOAKS).[15] The MOAKS is a semi-quantitative scoring method for knee OA features. Every feature is scored in predefined sub-regions of the knee joint. The features that we used in the current study are bone marrow lesions (BMLs), cartilage defects and osteophytes. In the MOAKS BMLs are scored according to the size of the BML with respect to the sub-region in which it is located. When the BML size was up to 33% of the sub-region, it was graded grade 1. BML sizes 33% to 66% were scored as grade 2. BMLs larger than 66% of the sub-region were scored grade 3. Cartilage defects are defined as loss of cartilage thickness as percentage of the surface area of a sub-region, where loss of less than 10% is scored as grade 1, loss of 10% to 75% as grade 2 and loss of more than 75% as grade 3. Osteophytes were graded as none (grade 0), small (grade 1), medium (grade 2) and large (grade 3). We scored meniscal tears as medial meniscal tear, lateral meniscal tear or both medial and lateral meniscal tear.

Two extensively trained researchers evaluated all MRI scans using the MOAKS. The baseline and follow-up MRI scans were analyzed at the same time and the order of measurements was known. All readers were trained to apply the MOAKS by a musculoskeletal radiologist with 15 years of experience. All doubtful findings were discussed with this radiologist, who made the final decision about the scoring.

Outcome measures

In reporting the outcomes we combined sub-regions of the MOAKS. We defined patellofemoral as a combination of the sub-regions patella medial, patella lateral, femur trochlea medial and femur trochlea lateral. Tibiofemoral medial was a combination of the sub-regions femur central medial, femur posterior medial, tibia anterior medial, tibia central medial and tibia posterior medial. Tibiofemoral lateral was a combination of the sub-regions femur central lateral, femur posterior lateral, tibia anterior lateral, tibia central lateral and tibia posterior lateral.

At baseline we reported the presence of BMLs, cartilage defects and osteophytes for the complete study population and for patients who had a 24-month MRI available.

At 24 months follow-up, we reported the change of BMLs compared to baseline, according to the definitions reported in Runhaar et al.[16] Progression of BMLs was defined as an increase in the number of BMLs in one sub-region or an increase in the size of the BML. Improvement of BMLs was defined as a decrease in the number of BMLs in one sub-region or as a decrease of the size of the BML. We did not assess subchondral cysts, since the number of cysts in our study population was considered low. We added a within-grade change to score the progression of BMLs. For example, if a BML changed from 40% of the sub-region to 60% of the sub-region, it would still be grade 2 according to the original MOAKS, but in our scoring system it was graded as progression. Progression and improvement of cartilage defects was defined using the same definitions as for BMLs. Progression of osteophytes was defined as an increase of the size of the osteophyte from grade 0 or 1 at baseline to grade 2 at follow-up, or from grade 2 at baseline to grade 3 at follow-up.

Data analysis

We used descriptive statistics to present the progression of early degenerative changes for the two randomization groups, arthroscopic partial meniscectomy and physical therapy (as randomized). We reported progression of BMLs, cartilage defects and osteophytes for the complete knee joint and for each sub-region. For BMLs and cartilage defects, we made flowcharts to visualize whether the BML or cartilage progression was because of an increase in size of the BML or cartilage defect, or because of the development of a new BML or cartilage defect at 24 months. We also presented the progression of BMLs, cartilage defects and osteophytes in an as-treated analysis for the following groups: arthroscopic partial meniscectomy, physical therapy + no surgery and delayed arthroscopic partial meniscectomy. Since this study was not powered for the current research question, we only performed descriptive statistical analysis.

RESULTS

Patients

Between 2014 and 2018, 100 patients were included in the STARR trial of which 99 were included in the current study, since 1 patient withdrew from the study. A 24-month MRI was available for 83% (n=40) of patients randomized to arthroscopic partial meniscectomy and 80% (n=41) of patients randomized to physical therapy. Baseline characteristics are presented in Table 1.

Sixteen patients (39%) of the physical therapy group (who had a 24-month MRI available) underwent a delayed arthroscopic partial meniscectomy during the follow-up period in consultation with the orthopedic surgeon, because of persistent complaints. Three patients randomized to the arthroscopic partial meniscectomy group did not undergo surgery, since complaints had resolved before surgery. BMLs, cartilage defects and osteophytes at baseline of patients who had a 24-month MRI were comparable to all patients as shown in Table 2.

Table 1. Baseline characteristics

	Arthroscopic partial meniscectomy (n = 48)	Physical therapy (n = 51)
Age at inclusion, years	34.1 (8.6)	35.6 (7.5)
Male sex, n (%)	37 (77)	38 (75)
BMI (kg/m²)	25.5 (4.2)	26.1 (4.6)
Activity level pre-injury (Tegner scale)[a]	6.5 (2.2)	6.4 (2.0)
Time between trauma and baseline MRI, days	88.2 (64.5)	83.8 (63.8)
Meniscus injured during, n (%)		
sport	27 (56)	27 (53)
daily activities	5 (10)	11 (22)
work	10 (21)	8 (16)
other	5 (10)	5 (10)
Meniscal tear baseline MRI, n (%)		
medial meniscus	31 (65)	35 (69)
lateral meniscus	16 (33)	14 (27)
medial + lateral meniscus	1 (2)	2 (4)

Data is presented as mean with standard deviation in brackets unless otherwise reported. Some characteristics of the arthroscopic partial meniscectomy group are known for 47 patients instead of 48. 1 patient had no baseline MRI.
a The Tegner scores ranges from 0 to 10, with higher scores indicating a higher activity level.

Table 2. BMLs, cartilage defects and osteophytes at baseline

	BML		Cartilage defect		Osteophyte	
	All patients (n=99)	24-month MRI available (n=81)	All patients (n=99)	24-month MRI available (n=81)	All patients (n=99)	24-month MRI available (n=81)
Total, n (%)	71 (72)	59 (73)	35 (35)	26 (32)	21 (21)	18 (22)
grade 1*	45 (46)	34 (42)	13 (13)	8 (10)	-	-
grade 2**	20 (20)	19 (23)	21 (21)	17 (21)	21 (21)	18 (22)
grade 3***	6 (6)	6 (7)	1 (1)	1 (1)	0 (0)	0 (0)

* worst grade present is grade 1
** worst grade present is grade 2
*** worst grade present is grade 3
BMLs = bone marrow lesions
Grade 0: none
Grade 1: <33% of sub regional volume
Grade 2: 33-66% of sub regional volume
Grade 3: >66% of sub regional volume
Cartilage defects
Grade 0: none
Grade 1: <10% of region of cartilage surface area
Grade 2: 10-75% of region of cartilage surface area
Grade 3: >75% of region of cartilage surface area
Osteophytes
Grade 0: none
Grade 1: small
Grade 2: medium
Grade 3: large

Progression of OA features – as randomized

Progression of BMLs, cartilage defects and osteophytes for the randomization groups is presented in Table 3. At 24 months 30% (n=12) of the patients randomized to arthroscopic partial meniscectomy showed BML progression, compared to 22% (n=9) of the patients randomized to physical therapy. Progression of cartilage defects was present in 40% (n=16) of the arthroscopic partial meniscectomy group, compared to 22% (n=9) of the physical therapy group. In the arthroscopic partial meniscectomy group progression of cartilage defects was present both in the patellofemoral and tibiofemoral subregions, while in the physical therapy group progression of cartilage defects was mainly present in the patellofemoral sub-region. Osteophyte progression was present in 18% (n=7) of the arthroscopic partial meniscectomy group and 15% (n=6) of the physical therapy group.

Table 3. 'As randomized' analysis of progression of BMLs, cartilage defects and osteophytes

	Arthroscopic partial meniscectomy (n = 40[a])	Physical therapy (n = 41[b])
BML progression, n (%)	12 (30)	9 (22)
only patellofemoral	3	3
only tibiofemoral medial	0	2
only tibiofemoral lateral	3	3
PF + TF medial	3	0
PF + TF lateral	2	0
TF medial + TF lateral	0	1
Cartilage defect progression, n (%)	16 (40)	9 (22)
only patellofemoral	7	6
only tibiofemoral medial	3	1
only tibiofemoral lateral	3	1
PF + TF medial	2	1
PF + TF lateral	1	0
TF medial + TF lateral	0	0
Osteophyte progression, n (%)	7 (18)	6 (15)
only patellofemoral	0	0
only tibiofemoral medial	4	5
only tibiofemoral lateral	2	1
PF + TF medial	1	0
PF + TF lateral	0	0
TF medial + TF lateral	0	0

BML = bone marrow lesion
PF = patellofemoral
TF = tibiofemoral
Progression of BMLs or cartilage defects was defined as an increase in the number of BMLs/cartilage defects in one sub-region or an increase in the size of the BML/cartilage defect. Improvement of BMLs/cartilage defects was defined as a decrease in the number of BMLs/

cartilage defects in one sub-region or as a decrease in the size of the BML/cartilage defect. Progression of osteophytes was defined as an increase of the size of the osteophyte or in the number of osteophytes.
a Of the 48 patients randomized to arthroscopic partial meniscectomy 40 patients had an MRI at 24 months.
b Of the 51 patients randomized to physical therapy 41 patients had an MRI at 24 months.

Details on BML and cartilage defect progression

Figure 1 presents the development of BMLs over time. Of the patients who had a BML on baseline, the BML showed progression at 24-month follow-up in 41% of the arthroscopic partial meniscectomy group compared to 23% of the physical therapy group. Of the patients who had no BML on baseline, 18% of the physical therapy group had a new BML at follow-up compared to 0% of the arthroscopic partial meniscectomy group.

Figure 2 presents the development of cartilage defects over time. Of the patients who had a cartilage defect on baseline, the cartilage defect showed progression at 24-month follow-up in 57% of the arthroscopic partial meniscectomy group compared to 42% of the physical therapy group. Of the patients who had no cartilage defect at baseline, 33% of the arthroscopic partial meniscectomy group had a new cartilage defect at follow-up compared to 14% of the physical therapy group.

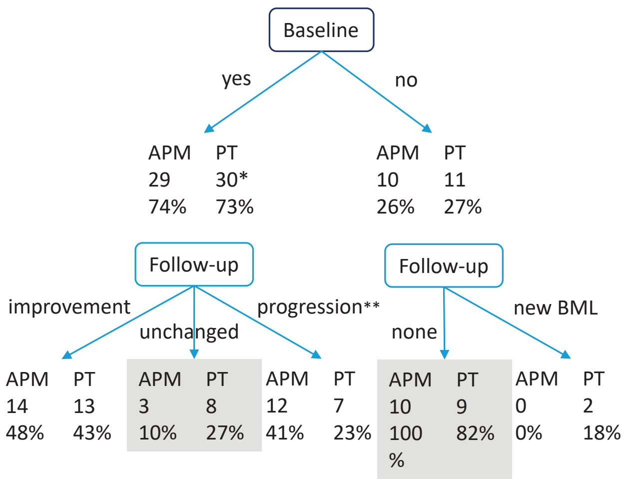

Figure 1. Flowchart of BML change

Baseline: presence of one or more BMLs at baseline (yes or no)
Follow-up: change of BMLs compared to baseline
APM = arthroscopic partial meniscectomy
PT = physical therapy
BML = bone marrow lesion
In the arthroscopic partial meniscectomy group, 1 patient is missing on baseline.
* 2 missing on follow-up
** includes patients with both improvement and progression of BMLs

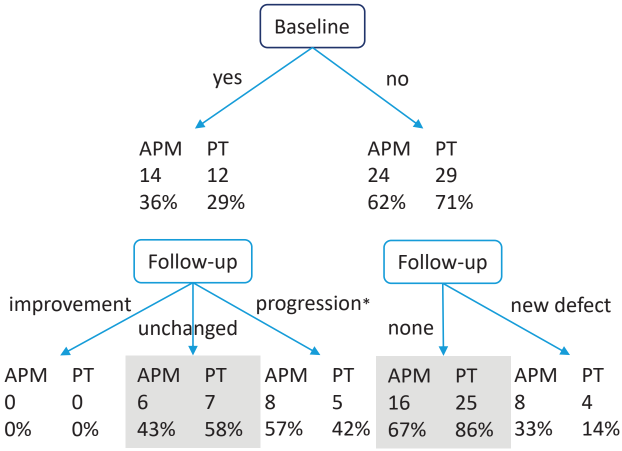

Figure 2. Flowchart of cartilage defect change

Baseline: presence of one or more cartilage defects at baseline (yes or no)
Follow-up: change of cartilage defects compared to baseline
APM = arthroscopic partial meniscectomy
PT = physical therapy
In the arthroscopic partial meniscectomy group, 2 patients are missing on baseline.
* includes patients with both improvement and progression of cartilage defects

Progression of OA features – as treated

Table 4 shows the progression of BMLs, cartilage defects and osteophytes for the different groups of the as treated analysis. Patients who had a delayed arthroscopic partial meniscectomy had BML progression comparable to patients who had an arthroscopic partial meniscectomy (31% vs. 32%). Progression of cartilage defects in patients who had a delayed arthroscopic partial meniscectomy was comparable to patients who had physical therapy or no surgery (19% vs. 21%).

Table 4. 'As treated' analysis of progression of BMLS, cartilage defects and osteophytes

	Arthroscopic partial meniscectomy (n=37)	Physical therapy + no surgery (n=28)	Delayed arthroscopic partial meniscectomy (n=16)
BML progression, n (%)	12 (32)	4 (14)	5 (31)
only patellofemoral	3	1	2
only tibiofemoral medial	0	1	1
only tibiofemoral lateral	3	1	2
PF + TF medial	3	0	0
PF + TF lateral	2	0	0
TF medial + TF lateral	0	1	0
Cartilage defect progression, n (%)	16 (43)	6 (21)	3 (19)
only patellofemoral	7	4	2
only tibiofemoral medial	3	0	1
only tibiofemoral lateral	3	1	0
PF + TF medial	2	1	0
PF + TF lateral	1	0	0
TF medial + TF lateral	0	0	0
Osteophyte progression, n (%)	7 (19)	4 (14)	2 (13)
only patellofemoral	0	0	0
only tibiofemoral medial	4	3	2
only tibiofemoral lateral	2	1	0
PF + TF medial	1	0	0
PF + TF lateral	0	0	0
TF medial + TF lateral	0	0	0

BML = bone marrow lesion
PF = patellofemoral
TF = tibiofemoral
Progression of BMLs or cartilage defects was defined as an increase in the number of BMLs/cartilage defects in one sub-region or an increase in the size of the BML/cartilage defect. Improvement of BMLs/cartilage defects was defined as a decrease in the number of BMLs/cartilage defects in one sub-region or as a decrease in the size of the BML/cartilage defect. Progression of osteophytes was defined as an increase of the size of the osteophyte or in the number of osteophytes.

DISCUSSION

In this secondary analysis of an RCT on young patients with traumatic meniscal tears we found more BML and cartilage defect progression at 24 months in patients allocated to arthroscopic partial meniscectomy compared to physical therapy with optional delayed arthroscopic partial meniscectomy. We also found more new cartilage defects after 24 months in patients randomized to arthroscopic partial meniscectomy compared to patients randomized to physical therapy.

In choosing the best treatment option for young patients with traumatic meniscal tears, it is important to know which treatment has the lowest risk for OA. The question is whether we should treat patients with direct surgery or initial physical therapy with optional delayed partial meniscectomy if the meniscal tear is not suitable for suture repair. Based on our recent RCT in young patients with traumatic meniscal tears, arthroscopic partial meniscectomy and physical therapy have similar clinical outcomes.[9] Moreover, based on the results of the current study, arthroscopic partial meniscectomy may lead to more degeneration of the knee joint compared to initial physical therapy with optional delayed arthroscopic partial meniscectomy. It is widely known that removal of the entire meniscus is a strong risk factor for the development of OA.[17] Current treatment of traumatic meniscal tears aims to save the meniscus by performing meniscal repair. When meniscal repair is not possible, an arthroscopic partial meniscectomy is performed. This study shows that preserving meniscus tissue with a partial meniscectomy in young patients with a traumatic meniscal tear is not enough to prevent OA. Starting with physical therapy and leaving the meniscal tear in situ instead does not seem to lead to more degenerative changes of the knee joint, at least within 24 months. Concerning both favorable clinical and radiological outcomes of initial physical therapy we should be careful with arthroscopic partial meniscectomy, also in treating isolated traumatic meniscal tears in young patients. This is consistent with the recent ESSKA guideline on treatment of traumatic meniscal tears that promotes saving the meniscus as much as possible.[5] We excluded patients with meniscal tears suitable for suture repair based on the baseline MRI. When meniscal repair is not possible, initial physical therapy is the best option to prevent OA based on the current study.

Although our RCT includes a homogenous study population with isolated traumatic meniscal tears without any radiographic OA, on the baseline MRIs most knees were not as healthy as expected (Chapter 6). A majority of the patients had one or more BMLs at baseline (72%) and 35% had a cartilage defect. This can either be a result of the impact of the trauma or may be a sign of early OA of the knee joint that was already present before the trauma. It is known that meniscal tears may be the symptom of early developing OA, this is also true for traumatic meniscal tears.[18] In our current study it is unclear whether the progression of degeneration of the knee joint at 24 months is the consequence of the meniscal tear, or if the degeneration that was already present at baseline progressed over time.

We found that the proportion of BMLs seen on MRI at 24 months was comparable between patients treated primarily with an arthroscopic partial meniscectomy and patients who had a delayed arthroscopic partial meniscectomy. Cartilage defects in patients who had delayed arthroscopic partial meniscectomy were comparable to patients who had no surgery or physical therapy. If arthroscopic partial meniscectomy would lead to additional BMLs and cartilage defects over time, you would expect that patients who had delayed meniscectomy would have BMLs and cartilage defects comparable to patients who had early surgery. Delayed arthroscopic partial meniscectomies were performed later during follow-up than early meniscectomies, this may explain why patients who had a delayed arthroscopic partial meniscectomy had a lower number of cartilage defects, since cartilage defects associated with OA usually develop later than BMLs.[19] Further degeneration of the knee joint in the delayed surgery group, including more cartilage defects, may develop over time. Long-term follow-up with MRI of these patients would be interesting to investigate if patients with delayed arthroscopic partial meniscectomy will indeed develop cartilage defects similar to patients with early surgery.

A strength of our study is that we studied a unique homogenous study population of young patients with isolated traumatic meniscal tears and without radiographic OA. To our knowledge there is only one other RCTs on young patients with traumatic meniscal tears, the DREAM trial, but this study has not published any MRI data.[20] Also most studies on older patients with degenerative meniscal tears have no MRI data at follow-up. Only one study published MRI data on 18- and 60-month follow-up of older patients with OA on baseline and a degenerative meniscal tear, showing that patients who had arthroscopic partial meniscectomy had more degenerative changes on MRI compared to patients who had physical therapy.[21, 22] These results are comparable to the results of our study.

A limitation of our study is that we only have an MRI at 24-month follow-up. This follow-up period is relatively short to investigate the development of OA. Based on this study we do know that there are already many degenerative changes in the knee joint during the first 24 months, especially in the patients who had arthroscopic partial meniscectomy. Since OA is an ongoing process, these degenerative changes will probably expand over time. Further follow-up of our study population will indicate whether there are differences in OA features between both treatment groups at the long term.

CONCLUSION

We found more progression of BMLs and cartilage defects with arthroscopic partial meniscectomy compared to physical therapy with optional delayed arthroscopic partial meniscectomy at 24-month follow-up in young patients with isolated traumatic meniscal tears without radiographic OA.

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Chapter 8

Discussion

This chapter will discuss all findings from previous chapters and will highlight future perspectives. It will address treatment of both anterior cruciate ligament (ACL) ruptures and traumatic meniscal tears.

The main goal in patient care is to provide treatment that offers the maximum health benefit based on the best available current evidence. Despite the absence of evidence demonstrating superior outcomes of surgery compared to initial physical therapy, the prevailing orthopaedic clinical practice worldwide predominantly involves operative treatment for ACL ruptures and traumatic meniscal tears. This thesis provides new insights on treatment of ACL ruptures and traumatic meniscal tears and aims to promote evidence based treatment for these traumatic knee injuries. We found that patients with ACL ruptures who failed non-operative treatment experienced instability complaints, pain during activity and a low perception of their knee function. The number of meniscal procedures did not differ between early ACL reconstruction and rehabilitation therapy with optional delayed ACL reconstruction. In young patients with traumatic meniscal tears included in the STARR trial we found that arthroscopic partial meniscectomy was not superior to physical therapy plus optional delayed arthroscopic partial meniscectomy. Arthroscopic partial meniscectomy was also not likely to be cost-effective in the treatment of young patients with traumatic meniscal tears. A majority of the patients of the STARR trial had posttraumatic and osteoarthritis (OA) related changes at baseline. At 24-month follow-up patients allocated to arthroscopic partial meniscectomy had more OA-related changes on MRI compared to patients allocated to initial physical therapy.

OPTIMAL TREATMENT OF ACL RUPTURES

Two large randomized controlled trials (RCTs) have been published on treatment of ACL ruptures, the COMPARE and KANON trial. Both trials found that initial non-operative treatment may serve as first-line treatment for patients with ACL ruptures.[1, 2] In both studies about half of the patients experienced an unsuccessful non-operative treatment and had a delayed ACL reconstruction during follow-up. Question is why part of the patients is unsuccessful with non-operative treatment and how we can recognize these patients in advance. In the COMPARE trial patients who failed non-operative treatment experienced instability complaints, pain during activity and a low perception of their knee function (Chapter 2). We also found that these patients were younger and had a higher pre-injury sport activity level. The most recent Dutch guideline on ACL ruptures recommends to discuss both operative and non-operative treatment with patients.[3] In the Netherlands patients have to be referred from their general practitioner to an orthopaedic surgeon. Often there is a delay between ACL injury and referral to the hospital. In this period patients usually start with non-operative treatment, like physical therapy. However, worldwide many orthopaedic surgeons perform an early ACL reconstruction, within 1 to 10 weeks after the injury. A commonly used argument is that delaying ACL surgery leads to persistent knee instability which limits a patients' daily activities and that it increases the risk for additional meniscal injuries. In the COMPARE trial the number of meniscal procedures during two-year follow-up in patients treated with rehabilitation therapy and optional delayed ACL reconstruction did not differ from patients who received early ACL reconstruction (Chapter 3). A limitation of these results is that we have no MRIs at follow-up of the COMPARE trial, so we have no data on the number of meniscal injuries that developed during follow-up. Also in the KANON trial there was no difference in meniscal surgeries at five-year follow-up.[4] As cost-effectiveness is also important in choosing the best treatment option, a cost-effectiveness analysis of the treatment of ACL ruptures has been published with use of the COMPARE data.[5] This analysis showed that ACL reconstruction for all patients is not likely to be cost-effective compared to rehabilitation plus optional delayed reconstruction. In conclusion, early ACL reconstruction is not necessary and not cost-effective for all patients and seems not to lead to additional meniscal injuries. Although some patients, the younger ones with higher pre-injury activity levels and more complaints like pain and instability, are unsuccessful with non-operative treatment. Interpretation of these results should consider that a limitation of an RCT is that it studies patients at group level. In clinical practice we are searching for the most optimal treatment for the individual patient. Future research should focus on finding the best treatment for individual patients, leading towards more patient tailored treatment.

OPTIMAL TREATMENT OF TRAUMATIC MENISCAL TEARS

To date high quality RCTs on young patients with traumatic meniscal tears were lacking. Therefore we designed the STARR trial, an RCT comparing two different treatment strategies in patients under 45 years of age with isolated traumatic meniscal tears. We showed that arthroscopic partial meniscectomy was not superior to physical therapy plus optional delayed arthroscopic partial meniscectomy (Chapter 4). Another RCT on treatment of traumatic meniscal injuries was published at about the same time as the STARR trial. Skou et al found in this RCT (the DREAM trial) that in young active adults with meniscal tears early meniscal surgery was not superior to a strategy of exercise and education with the option of later surgery.[6] Patients in the DREAM trial were slightly younger compared to patients in the STARR trial (mean age of 30 vs. 35 years). Our STARR trial focused on including a homogenous patient group with recent isolated traumatic tears without radiological OA. We excluded meniscal tears suitable for suture repair based on MRI, although meniscal repair was allowed when the tear turned out to be suitable for suture repair during the arthroscopy based on perioperative findings. In the DREAM trial all meniscal tears, without additional complete ruptures of any knee ligament, were included and randomization to surgery included both arthroscopic partial meniscectomy and meniscal repair, depending on the decision of the orthopaedic surgeon during surgery. Both RCTs excluded patients with a locking knee. So although both the STARR and DREAM trial studied young patients with meniscal tears, they differ in the fact that the DREAM trial was more pragmatic and included all patients with meniscal tears without ligament injuries, while the STARR trial aimed to include only patients with isolated traumatic meniscal tears without radiographic OA. Nevertheless both RCTs found that early meniscal surgery was not superior to initial non-operative treatment with optional delayed meniscal surgery. The STARR trial, together with similar findings from the DREAM trial, provides high quality evidence that non-operative treatment may be the first-line treatment in young patients with meniscal tears. Combining this with the fact that arthroscopic partial meniscectomy for all patients is also unlikely to be cost-effective (Chapter 5), orthopaedic surgeons should critically review if standard surgical treatment of young patients with a traumatic meniscal tear is still justified. Of course long term evaluation will have to show how clinical results of non-operative treatment develop over time. We should also investigate why 41% of the patients failed non-operative treatment and underwent delayed arthroscopic partial meniscectomy. Are these patients experiencing pain or other knee complaints, do they develop mechanical symptoms or does the type or location of the meniscal tear play a role? There are some indications that lateral meniscal tears have a better prognosis with non-operative treatment than medial meniscal tears.[7] Question is how we can identify patients who need surgery in an early stage to prevent that they have a period of unsuccessful non-operative treatment with persistent complaints and inability to perform at their desired activity level.

In treating patients with traumatic meniscal tears another goal is to choose the best treatment option for preserving quality of the knee joint, taking into account the effect of different treatments on developing OA. Short term results at 24 months follow-up showed that patients allocated to arthroscopic partial meniscectomy had more OA-related features on MRI compared to patients allocated to initial non-operative treatment (Chapter 7). Concerning favourable clinical, radiological and cost-effectiveness outcomes of initial physical therapy we should be careful with arthroscopic partial meniscectomy when treating isolated traumatic meniscal tears in young patients. Interpretation of the STARR trial should consider that it is an RCT and provides evidence at group level. The best treatment may be different for each individual patient, depending on one's individual needs and wishes.

TRAUMATIC MENISCAL TEAR IN A HEALTHY KNEE JOINT OR IN AN EARLY STAGE OF OA?

The goal of the STARR trial was to include patients with isolated traumatic meniscal tears in healthy knee joints, so without any radiographic OA. On the baseline MRIs most knees were not as healthy as expected. A majority of the patients had posttraumatic and OA-related changes at baseline (Chapter 6). This questions whether these changes can be contributed to the trauma or to beginning OA. For example, bone marrow lesions can occur at the location of a direct trauma or may show typical patterns matching various indirect trauma mechanisms, but may also be present in the osteoarthritic knee joint.[8, 9] Whether a bone marrow change or cartilage defect is related to the trauma or OA cannot be distinguished on MRI.[10] Since MRI cannot distinguish between posttraumatic and OA-related abnormalities it is still unclear if the changes on MRI we found are related to the trauma or that patients from the STARR trial already had some degree of OA, although not visible on radiographs. In our study it is unclear what the impact of the meniscal tear was on the progression of degeneration of the knee joint at 24 months. It is known that meniscal tears can be the symptom of early developing OA, this is also true for traumatic meniscal tears.[11] It is thought that the chance of getting a meniscal tear depends on the degree of degeneration of the meniscus, so the higher the degree of meniscal degeneration the higher the chance for a meniscal tear with a certain traumatic event. Potentially some patients from the STARR trial sustained their meniscal tear as a first expression of beginning OA, as meniscal tissue in beginning OA is more vulnerable and more susceptible to tear.[11] In that case part of the patients may have had a more degenerative meniscal tear instead of a true traumatic meniscal tear, although radiographs showed no OA. The age limit of 45 years may have been too high to include a study population without any degeneration of the knee joint. Another theory can be that most of the traumatic meniscal tears, considered traumatic since symptoms started after a trauma and in knees without OA on radiographs, are not truly traumatic but a first sign of early OA. There seems to be a gradual change in meniscal degeneration over time, where the meniscus is more and more susceptible to tear in a traumatic event with increasing meniscal degeneration over time. This would implicate that there is not a clear difference between traumatic or degenerative tears, but more a gradual scale from healthy meniscal tissue with a tear, to meniscal tissue with some degeneration as sign of early OA to a complete degenerative meniscus in a knee joint with end stage OA. This may explain why a part of the patients in the STARR trial who started with non-operative treatment had satisfying clinical results after 24-month follow-up and did not need meniscal surgery, comparable to results of non-operative treatment of degenerative meniscal tears in older patients. Further research should focus on which patients benefit from meniscal surgery and who can manage with non-operative treatment.

LIMITATIONS OF COMPARE AND STARR TRIAL

A limitation of both the COMPARE and STARR trial is the potential presence of recruitment bias, since part of the patients declined to participate, in both trials 50 percent, because of a strong preference for one of the treatment arms. In the COMPARE trial these treatment preferences were equally divided, so they will probably not have influenced the outcome of the study. In the STARR trial a majority of the patients that declined to participate had a preference for operative treatment, so our results may therefore not apply to those with strong treatment preference. A general limitation of surgical RCTs is that there is a strong selection of patients who are included in the trial. After applying the predefined in- and exclusion criteria, patients may have a preference for one of the treatments and in some cases also the surgeon has a preference for a certain treatment or the idea that he or she can predict which patients may benefit from which treatment. This high chance of selection bias is an important limitation of RCTs and therefore results from RCTs have not always a high generalisability. Further research should consider alternative study designs that include all eligible patients to increase the generalisability of results.[12] On the other hand, RCTs also have many advantages, for example the lack of treatment allocation bias. Especially in treating acute knee traumas it is hard to perform an RCT. In both the COMPARE and STARR trial we succeeded to perform an RCT in a difficult traumatic setting, these types of RCTs are rare and provide important information.

In the analysis of patients who had delayed ACL reconstruction in the COMPARE trial a limiting factor is that every decision to perform surgery is not completely objective for both the orthopaedic surgeon and the patient. This is also true for the STARR trial. Not all aspects of this decision making can be objectified. This raises the question whether undergoing delayed surgery is indeed because of failing non-operative treatment. Or is this the result of multiple factors, both objective and subjective, from patient and surgeon, leading to the decision of delayed surgery. We found that patients who had delayed ACL reconstruction in the COMPARE trial, and thus 'failed' non-operative treatment, had lower International Knee Documentation Committee (IKDC) scores during follow-up compared to patients that had only physical therapy (Chapter 2). At 24-month follow-up these patients with delayed ACL surgery had slightly lower IKDC scores compared to all other patients in the study.[2] This raises the question if the delayed ACL surgery in patients who started with non-operative treatment is effective. Are these patients really better off with their surgery or would they have reached similar clinical results without surgery? It is also possible that there is a subgroup of patients that is unresponsive, so both unsuccessful with operative and non-operative treatment. For example these patients may have such a high desired activity level, that they are unable to cope with any symptoms of their knee. Question is whether unresponsive patients who fail non-operative treatment should have a delayed ACL reconstruction or that we have to accept that in some patients any therapy will lead to unsatisfactory results because of multiple factors, like too high expectations or sensitisation. Also in patients who receive early ACL reconstruction there will be patients who are not satisfied with the result of their treatment. It would be relevant to recognize these unresponsive patients before starting treatment, to prevent them from an unnecessary surgery with risk of complications. As mentioned before, further research should focus on gaining more insight in which patients benefit from which treatment.

In secondary analyses on a RCT it should be considered that the study was not initially powered to answer research questions other than the research question the study was designed for. An RCT is designed and powered to answer a predefined research question on group level and compares two randomization groups. Analysis of subgroups or other outcomes than the predefined outcomes have the risk of bias and results may not be reliable.

A limitation of the STARR trial is that we excluded patients with a meniscal tear suitable for suture repair based on MRI, but four patients that were randomized to arthroscopic partial meniscectomy had a meniscal repair because of perioperative findings. If a meniscal tear is suitable for suture repair, meniscal repair is also a treatment option in patients with traumatic meniscal tears.[7] Since we did not include meniscal repair as a treatment arm in our RCT, results from the STARR trial may not be applicable for patients with a meniscal tear suitable for suture repair.

GROUP LEVEL VERSUS INDIVIDUAL DECISIONS

Both the COMPARE and STARR trial provide conclusions for the complete study population, as both are RCTs designed to answer questions at group level. The decision to operate or to start with conservative therapy will always be an individual decision of every patient, together with their orthopaedic surgeon. This decision depends on a patient's individual symptoms, expectations and desires for his or her activity level and also on prognostic variables. In an ideal world an orthopaedic surgeon would predict which patients need ACL reconstruction or surgical treatment of their traumatic meniscal tear.

For ACL ruptures we found that patients who failed non-operative treatment were younger and had a higher pre-injury activity level (Chapter 2). Also other literature describes that patients with a lower age and higher activity level, especially performing pivoting sports, need an ACL reconstruction.[13-18] For traumatic meniscal tears almost all patients receive surgical treatment so no literature is available on predicting which patient needs surgery. In older patients with degenerative meniscal tears an extensive survey among experienced orthopaedic surgeons revealed that surgeons are unable to predict who will benefit from surgery.[19] In this study of van de Graaf et al 194 orthopaedic surgeons received 20 patient profiles of middle-aged patients with a symptomatic non-obstructive meniscal tear and predicted the expected change in knee function for two treatments (arthroscopic partial meniscectomy and exercise therapy). Fifty percent of the predictions were correct, so comparable to the percentage expected by chance. So although orthopaedic surgeons often think they can predict which treatment is best for their patient, it seems that this is more difficult than expected. Future research will have to elucidate which patients with ACL ruptures or traumatic meniscal tears benefit from surgery and who can manage with non-operative treatment, for example by designing an algorithm to help with each separate decision in each individual patient. In the COMPARE trial patients who failed non-operative treatment experienced instability complaints, pain during activity and had a low perception of their knee function before they underwent delayed ACL reconstruction (Chapter 2). So not only patient characteristics play a role in deciding to undergo ACL reconstruction, patient reported outcome measures (PROMs) are also important. Including PROMs in follow-up of patients with an ACL rupture may indicate in an early stage if someone is experiencing problems during non-operative treatment and may have to undergo ACL reconstruction. For both ACL ruptures and traumatic meniscal tears more focus on PROMs and patients' experienced complaints may help to distinguish which patients need surgery. Developing accurate treatment algorithms requires big data, there is a huge challenge in collecting usable data.

FUTURE PERSPECTIVES

This thesis provides new insights in the when, who and why of failing non-operative treatment in patients with a primary ACL rupture. Future research should focus on further characterizing these patients and also on ways to predict what treatment is best for each individual patient. Based on the aspects we found during decision making for ACL surgery, development of follow-up programs of ACL injured patients should not only focus on objective measures such as laxity but also on PROMs, expectations and desires of each individual patient. Currently, a new RCT of our group is ongoing to evaluate the effectiveness and cost-effectiveness of a treatment algorithm for patients with a complete primary ACL rupture.[20] To search for a more patient-tailored treatment and to design decision models we will probably need big data from large databases and artificial intelligence. A challenge in designing these decision models is what end points should be chosen. This starts with defining when a certain treatment is successful or not. Should this be for example a patient acceptable symptom status with a minimal IKDC score, quality of life score, return to sport, different functional tests, cartilage quality or level of knee OA? Further research on developing decision models should use clearly defined end points and definitions of successfulness of a treatment.

Eventually, this personalized medicine should also be incorporated in treating young patients with isolated traumatic meniscal tears. Before such a paradigm shift is possible, results of the STARR trial should first be further implemented in clinical practice, for example with standard non-operative treatment in young patients with traumatic meniscal tears. Further research should focus on long-term follow-up of this patient group to investigate whether the patients with non-operative treatment indeed maintain good clinical and radiological results. As our MRI data at 24 months indicated that non-operative treatment of traumatic meniscal tears may be the best treatment to prevent OA of the knee joint, question is what happens to the meniscal tear itself and the meniscal tissue in the long-term. Further research should investigate how these conservatively treated meniscal tears develop over time and how tissue quality of these menisci develops. This may help to choose the best treatment option in patients with traumatic meniscal tears. Changing clinical practice will be an enormous effort, but the STARR trial is a first step towards a more evidence-based approach of treatment of isolated traumatic meniscal tears.

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Chapter 9

Appendices

Appendix 1. Physical therapy protocol and home exercises
Appendix 2. Secondary outcomes for as randomized analyses during follow-up
Appendix 3. Estimated IKDC score for as treated analyses per measurement period

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STARR-trial Physical Therapy Protocol

Phase	Goal	Activities
I	Reduce knee effusion	Explanation and education about meniscal injury; advice for daily activities and to stay in 'pain free range of motion'
		Exercises (partial weight bearing) within 'pain free range of motion', e.g. walking, cross-training, cycling
IIa	Optimize range of motion	Transfers: sit and to stand Cycling Optional: stair walking (patient dependent)
		Homework: Extension and flexion -Straighten and bend the knee Practicing simple daily activities -Squat, step up, pelvic bridge
IIb	Optimize coordination and muscle function	To maintain / improve gait -Active dynamic gait To improve muscle function of the quadriceps To train proprioception
		Homework: Pursue full (passive) extension Practicing simple daily activities -Squat, step up, pelvic bridge
III	Stimulate activities in daily living and return to sport	Dependent on patients preferences / background / work situation: daily life or sport specific exercises
		<u>Daily life-specific exercises :</u> Walking and turning Kneeling, squatting, lifting Practicing complex, multiple transfers Practicing complex daily activities (e.g. turn + reach)
		<u>Sport-specific exercises :</u> Extended gait training (goal: increase of intensity), e.g. dribbling – skippings Jumping
		Homework: Practicing complex, multiple transfers Practicing complex daily activities (e.g. turn + reach)

Home exercises for meniscal tear

Ask your physical therapist for advice and support

Walking on a treadmill

- Start with walking
- Hold the rails if necessary
- Ask your physical therapists for advice on speed and technique

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Cycling on an exercise bike

- Adjust the bike to achieve a comfortable position
- Ask your physical therapist for advice on the cycling speed and changing the saddle height to increase bending of your knee

9

Get up from a chair (squat)

- Use a chair on a flat floor
- Sit down with a straight back with your knees in a 90 degrees angle
- Put your arms straight out (figure 1)
- Keep your knees pointing forwards, avoid a knocked knee position (figure 3)
- Stand up, while keeping your knees and arms pointing forwards, until your legs are straight (figure 2)
- Repeat this exercise 15 times, two to three times a day
- When you succeed in this exercise, adjust the exercise by placing the foot of your injured leg slightly backwards (see figure 4) and perform the exercise in the same way

Figure 1

Figure 2

Figure 3

Figure 4

Straighten the leg (extension)

- Use a bench approximately 40 centimeters high
- Place your hands on the bench, shoulder width apart, with your knees bent
- Elevate your uninjured leg (figure 1) while keeping your hands on the bench
- Pay attention to your knees, keep them pointing forwards, don't let your knees knock (figure 5)
- Straighten the injured leg (standing leg), while keeping your hands on the bench (figure 2)
- Repeat this exercise 10 times, two to three times a day
- When you succeed in this exercise, adjust the exercise by using a lower bench (20 centimeters) and perform the exercise in the same way (figure 3 and 4)

Figure 1

Figure 2

Figure 3

Figure 4

Figure 5

9

Step-up

- Use a bench or chair at knee-height (if this is too hard, use a lower bench or chair)
- Stand in front of the bench
- Keep your uninjured leg straight on the floor and place your injured leg on the bench while bending your injured knee (figure 1)
- Step up onto the bench, by straightening your injured leg and elevating your uninjured leg to 90 degrees. Pay attention to your injured leg, it has to be straightened completely.
- Pay attention to the knee of your injured leg, it has to point forwards, not go into a knocked knee position (figure 3)
- Keep your back straight and keep looking forwards (figure 4)
- Repeat this exercise 10 times, two to three times a day

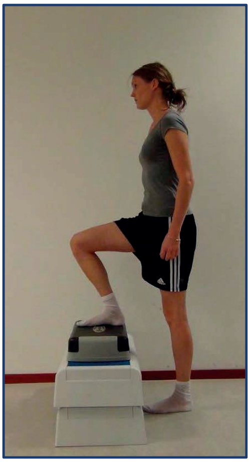


Figure 1

Figure 2

Figure 3

Figure 4

9

Pelvic bridge

- Lay down with your arms at your sides
- Bend your knees to an angle of 110 degrees (figure 1)
- Keep your feet flat on the floor
- Keep your head on the floor
- Lift your pelvis, while keeping your feet, arms and head on the floor (figure 2)
- Keep your upper legs in a straight line with your belly
- Hold this position for 5 seconds
- Repeat this exercise 15 times, two to three times a day, for three weeks in a row
- After 3 weeks and when you succeed in this exercise, you can adjust the exercise by straightening the injured leg and placing your arms in front of you (figure 3). Repeat this exercise 15 times, two or three times a day

Figure 1

Figure 2

Figure 3

Turn and reach

- Use a weight or water bottle of 0.5 to 1 kilograms
- Stand with your legs hip-width apart and place the weight on the side of the injured leg
- Move your uninjured leg back, with your toes still touching the floor (figure 1)
- Reach down with your arm from the uninjured side to the weight, while slightly bending your injured leg (figure 2)
- Grab the weight and straighten your injured leg, while keeping your uninjured leg with the toes on the floor (figure 3) until you are in the starting position again
- Repeat this exercise 10 times, two to three times a day
- When you can easily do in this exercise, make it harder by lifting your uninjured leg of the floor during the exercise (figure 4, 5 and 6)

Figure 1

Figure 2

Figure 3

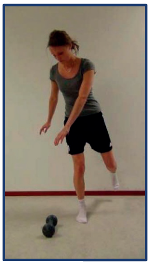


Figure 4

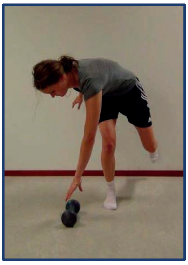


Figure 5

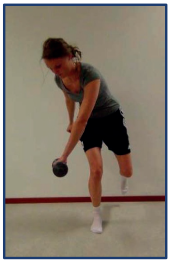


Figure 6

APPENDIX 2 - SECONDARY OUTCOMES* FOR AS RANDOMIZED ANALYSES DURING FOLLOW-UP

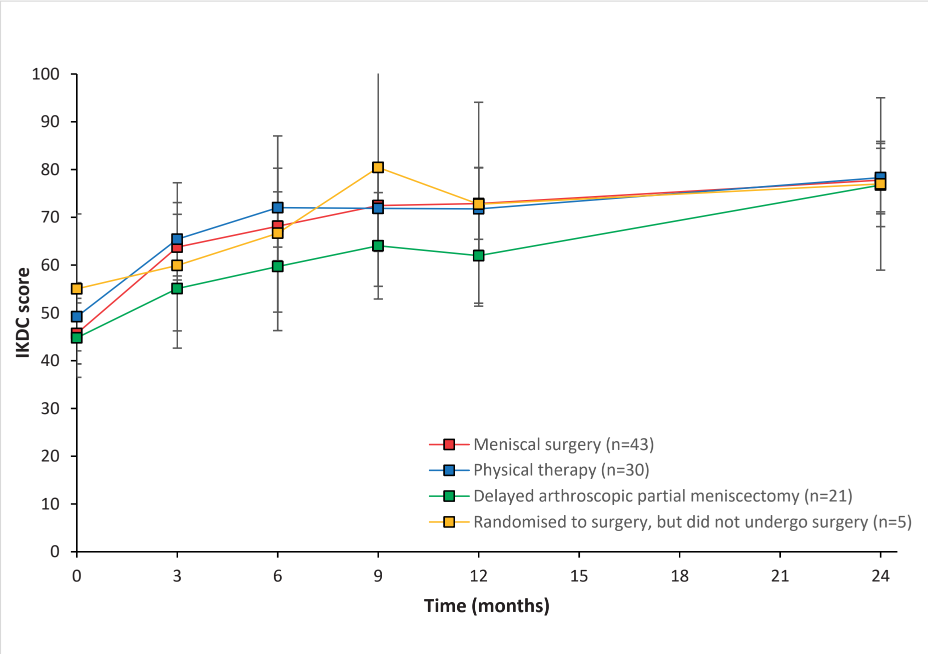
	Arthroscopic partial meniscectomy	Physical therapy	Between group difference
KOOS baseline			
pain	54.1 (48.2; 60.1)	59.5 (53.8; 65.2)	
symptoms	55.6 (49.7; 61.5)	62.9 (57.3; 68.5)	
ADL	61.3 (55.0; 67.6)	68.9 (62.9; 75.0)	
sport	30.2 (22.4; 38.0)	34.9 (27.4; 42.4)	
QoL	33.7 (28.0; 39.3)	35.4 (30.0; 40.8)	
KOOS 24 months			
pain	85.7 (79.0; 92.4)	83.8 (77.4; 90.2)	1.9 (-5.7; 9.6)
symptoms	81.8 (75.4; 88.2)	81.4 (75.2; 87.5)	0.5 (-6.6; 7.5)
ADL	92.0 (86.6; 97.5)	89.2 (84.1; 94.4)	2.8 (-3.3; 8.9)
sport	70.1 (60.5; 79.7)	69.3 (60.1; 78.6)	0.8 (-12.5; 14.0)
QoL	67.2 (59.1; 75.3)	65.8 (58.0; 73.6)	1.4 (-9.3; 12.0)
NRS rest			
baseline	3.9 (3.1; 4.6)	2.9 (2.2; 3.7)	
3 months	1.8 (1.1; 2.5)	1.6 (0.9; 2.2)	0.3 (-0.5; 1.0)
6 months	2.0 (1.2; 2.8)	1.3 (0.6; 2.1)	0.6 (-0.3; 1.6)
9 months	1.8 (0.8; 2.7)	1.5 (0.7; 2.4)	0.2 (-0.8; 1.3)
12 months	1.5 (0.6; 2.4)	1.7 (0.9; 2.6)	-0.2 (-1.2; 0.8)
24 months	1.2 (0.4; 1.9)	1.2 (0.5; 2.0)	-0.1 (-0.8; 0.7)
NRS activity			
baseline	6.6 (5.9; 7.3)	6.2 (5.5; 6.8)	
3 months	4.0 (3.2; 4.8)	3.8 (3.1; 4.6)	0.1 (-0.9; 1.1)
6 months	3.6 (2.7; 4.6)	2.9 (2.0; 3.8)	0.8 (-0.5; 2.0)
9 months	2.8 (1.7; 3.8)	3.1 (2.1; 4.0)	-0.3 (-1.7; 1.1)
12 months	2.4 (1.4; 3.3)	3.4 (2.5; 4.3)	-1.0 (-2.2; 0.2)
24 months	2.8 (1.9; 3.7)	2.4 (1.5; 3.3)	0.4 (-0.8; 1.5)
Lysholm			
baseline	66.9 (61.3; 72.5)	70.0 (64.7; 75.3)	
12 months	88.0 (82.3; 93.7)	83.0 (77.5; 88.4)	5.0 (-1.9; 11.9)
24 months	89.4 (84.8; 93.9)	88.3 (83.6; 93.1)	-1.0 (-6.2; 4.1)
WOMET			
baseline	38.1 (31.9; 44.4)	42.6 (36.6; 48.5)	
3 months	59.8 (51.9; 67.6)	59.4 (52.0; 66.8)	0.4 (-8.7; 9.5)
6 months	62.7 (54.8; 70.7)	65.8 (58.2; 73.4)	-3.1 (-12.4; 6.2)
9 months	71.9 (63.2; 80.7)	66.2 (58.2; 74.3)	5.7 (-4.8; 16.3)
12 months	70.8 (62.3; 79.3)	65.3 (57.1; 73.5)	5.5 (-4.9; 16.0)
24 months	71.9 (63.5; 80.2)	75.6 (67.6; 83.7)	-3.8 (-13.8; 6.2)

Continued.

	Arthroscopic partial meniscectomy	Physical therapy	Between group difference
Tegner**			
baseline	6.5 (5.9; 7.1)	6.4 (5.8; 7.0)	
3 months	3.8 (3.2; 4.5)	3.8 (3.2; 4.4)	0.0 (-0.8; 0.9)
6 months	4.6 (3.9; 5.4)	4.1 (3.4; 4.8)	0.6 (-0.4; 1.6)
9 months	5.0 (4.2; 5.8)	5.3 (4.5; 6.1)	-0.3 (-1.4; 0.8)
12 months	5.5 (4.8; 6.3)	4.4 (3.6; 5.1)	1.1 (0.1; 2.2)
24 months	5.4 (4.7; 6.1)	5.0 (4.4; 5.7)	0.3 (-0.6; 1.3)
Satisfaction with knee function			
baseline			
24 months	71.6 (63.7; 79.6)	70.1 (62.4; 77.8)	1.5 (-9.3; 12.3)

Data is presented as mean and 95% confidence interval between parentheses.
* adjusted for surgeon
** Tegner baseline score is pre-trauma score
Percentage of outcome available per time point: baseline 98%, 3 months 77%, 6 months 70%, 9 months 63%, 12 months 75%, 24 months 91%.

APPENDIX 3 - ESTIMATED IKDC SCORE* FOR AS TREATED ANALYSES PER MEASUREMENT PERIOD



	baseline	3 months	6 months	9 months	12 months	24 months
Meniscal surgery (n=43)	46 (39 to 52)	64 (57 to 71)	68 (61 to 75)	72 (64 to 81)	73 (65 to 80)	78 (71 to 84)
Physical therapy (n=30)	49 (42 to 56)	65 (58 to 73)	72 (64 to 80)	72 (63 to 81)	72 (63 to 80)	78 (71 to 86)
Delayed arthroscopic partial menisectomy (n=21)	45 (37 to 53)	55 (46 to 64)	60 (50 to 69)	64 (53 to 75)	62 (52 to 72)	77 (68 to 85)
Randomised to surgery, but did not undergo surgery (n=5)	55 (39 to 71)	60 (43 to 77)	67 (46 to 87)	80 (56 to 105)	73 (51 to 94)	77 (59 to 95)
Primary outcome available, %	*98*	*77*	*70*	*63*	*75*	*91*

* adjusted for surgeon
Error bars represent 95% confidence intervals

9

Chapter 10

Summary
Dutch Summary (Nederlandse samenvatting)
List of publications
PhD portfolio
Curriculum Vitae
Dankwoord

SUMMARY

Traumatic knee injuries frequently occur among young active people. Common injuries are an anterior cruciate ligament (ACL) rupture and a traumatic meniscal tear.

ACL ruptures are typically treated with a surgical ACL reconstruction. As of now, two large randomized controlled trials (RCTs) have been performed, comparing the effectiveness of operative and non-operative treatment of ACL ruptures. Both studies showed that some of the patients with an ACL rupture can achieve good clinical results with physical therapy alone and do not need a surgical ACL reconstruction. A subset of patients who were treated with physical therapy experienced unsuccessful outcomes and needed an ACL reconstruction at a later time point during follow-up. A common objection to conservative treatment or delayed reconstruction for ACL ruptures is the concern that persistent knee joint instability could result in more damage such as meniscal tears. This thesis explores why some patients with ACL ruptures fail non-operative treatment and investigates whether non-operative treatment or delayed surgery in ACL ruptures is associated with increased incidence of meniscal injuries. We used data from the COMPARE trial, one of the two RCTs on patients with ACL ruptures, to investigate this. The COMPARE trial included 167 patients with an ACL rupture of which 85 patients were randomized to early ACL reconstruction and 82 patients randomized to rehabilitation therapy with the option for delayed ACL reconstruction. Of these 82 patients 41 patients had a delayed ACL reconstruction during the 2-year follow-up period. *Chapter 2* describes why, when and which patients had a delayed ACL reconstruction. To investigate this we collected different patient-reported outcome measures: the International Knee Documentation Committee (IKDC), pain score and experienced knee instability. The IKDC measures a patient's perception of their symptoms, knee function and ability to participate in sports activities, with 100 as optimal score and 0 as lowest score. Most patients had their delayed ACL reconstruction 3 to 6 months after inclusion with instability of their injured knee as the most common reason for surgery. A majority of the patients who had delayed ACL reconstruction reported an IDKC below 60, pain scores of 3 or higher and experienced knee instability complaints. During follow-up patients who had delayed ACL reconstruction had lower IKDC scores and higher pain scores compared to patients who were successful with rehabilitation therapy, adjusted for sex, age and BMI. Patients who had delayed ACL reconstruction were significantly younger and had a higher pre-injury activity level compared to patients who were successful with non-operative treatment. This is the first study that describes why, when, and which patients with an ACL injury who started with non-operative treatment received an ACL reconstruction in an RCT setup.

In *chapter 3* we investigate whether non-operative treatment of ACL ruptures results in a higher incidence of meniscal injuries in comparison to operative treatment using

data from the COMPARE trial. We compared the number of meniscal surgeries between two groups: patients randomly assigned to early ACL reconstruction (n=85) and those assigned to rehabilitation therapy with the option for delayed ACL reconstruction (n=82). We compared the incidence of meniscal surgeries over the 2-year follow-up period between the two randomization groups. The analysis was adjusted for sex, BMI, age and orthopaedic surgeon involved. At baseline 41% of the entire study population (69 out of 167) had a meniscal tear on MRI. During the 2-year follow-up 29% (25 out of 85) of the patients randomized to early ACL reconstruction had a meniscal procedure, compared to 21% (17 out of 82) of the patients randomized to rehabilitation plus optional delayed reconstruction. The risk ratio was 0.67 with 95% confidence interval 0.40 to 1.12, p-value 0.12. Of the patients who received early ACL reconstruction (n=82) and those who received delayed ACL reconstruction (n=41), 5% in each group required an additional isolated meniscal procedure after ACL reconstruction. Among patients who did not undergo ACL reconstruction (n=41), 10% (n=4) required an isolated surgical procedure for a meniscal tear during the 2-year follow-up period. In this study we conclude that initial non-surgical treatment of ACL ruptures with optional delayed ACL reconstruction does not lead to a higher number of meniscal procedures than early ACL reconstruction during the 2-year follow-up period.

Traumatic meniscal tears in young patients are usually treated surgically although currently, there is a lack of high-quality evidence supporting the superiority of meniscal surgery over non-operative treatments. Therefore we designed and performed the STARR trial, a multicenter RCT focusing on patients aged 18-45 years with a recent onset, traumatic, MRI-verified, isolated meniscal tear without knee osteoarthritis (OA). Patients were randomized to either arthroscopic partial meniscectomy or standardized physical therapy, with option for delayed arthroscopic partial meniscectomy after 3 months of follow-up. *Chapter 4* describes the clinical outcomes of the STARR trial. The primary outcome was the IKDC score at 24 months. Between 2014 and 2018, 100 patients were included with a mean age of 35. Arthroscopic partial meniscectomy was assigned to 49 patients and 51 were allocated to physical therapy. Within the physical therapy group, 21 patients (41%) received delayed arthroscopic partial meniscectomy during the follow-up period. In both groups, improvement in IKDC scores was clinically relevant during follow-up compared to baseline scores. At 24 months, the mean IKDC score was 78 (95% confidence interval 71 to 84) in both the arthroscopic partial meniscectomy group and the physical therapy group with a between-group difference of 0.1 (95% confidence interval -7.6 to 7.7). Based on these findings from the STARR trial involving young patients with isolated traumatic meniscal tears, we conclude that at 24-month follow-up, early arthroscopic partial meniscectomy is not superior to a strategy of physical therapy with optional delayed arthroscopic partial meniscectomy.

When determining the optimal treatment, we consider not only the clinical outcomes but also the cost-effectiveness of treatments. Therefore we also performed a cost-effectiveness analysis of the STARR trial. This analysis compares the cost-effectiveness of arthroscopic partial meniscectomy and physical therapy in patients included in the STARR trial. The findings of this cost-effectiveness analysis are presented in *chapter 5*. Cost-utility was calculated as the incremental costs per quality-adjusted life year (QALY) gained for arthroscopic partial meniscectomy compared to physical therapy. Calculations were performed from a healthcare system perspective and a societal perspective. On average, over 24 months, patients in the arthroscopic partial meniscectomy group had a 0.005 QALYs lower quality of life, with 95% confidence interval -0.13 to 0.14. The cost-utility ratio was €-160,000/QALY from the healthcare perspective and €-223,372/QALY from the societal perspective. This indicates that arthroscopic partial meniscectomy incurs additional costs, whereas no health benefit is produced. This analysis concludes that arthroscopic partial meniscectomy is not likely to be cost-effective in treating young patients with isolated traumatic meniscal tears.

In *Chapter 6* posttraumatic and OA-related lesions on MRI in young patients with isolated traumatic meniscal tears are presented. The study includes patients from the STARR trial and healthy controls. Baseline MRIs of patients and controls were analyzed using the MRI Osteoarthritis Knee Score (MOAKS). We reported bone marrow lesions (BMLs), cartilage defects and osteophytes for patients and controls. Additionally, the overlap between meniscal tear location and BMLs was presented in the patients group. At baseline 72% of the patients (n=72) had one or more BMLs, in contrast to 44% of the controls (n=22). More severe BMLs were predominantly observed in patients, a trend also noted for cartilage defects. Osteophytes, on the other hand, were equally prevalent in patients as in controls. Half of the patients had a BML in the same compartment as their meniscal tear. This study, which examined MRI findings in patients with isolated traumatic tears, revealed more pronounced BMLs and cartilage defects in patients compared to controls.

In addition to evaluating the clinical and cost-effectiveness outcomes of the STARR trial, *Chapter 7* studies the impact of the two different treatments on knee degeneration. The chapter compares early degenerative changes on MRI at 24 months in patients treated with arthroscopic partial meniscectomy versus physical therapy with optional delayed arthroscopic partial meniscectomy. MRIs at baseline and 24 months were scored using the MOAKS. The outcome measured was the progression of BMLs and cartilage defects after 24 months. Our findings at 24 months revealed more progression of both BMLs and cartilage defects in patients randomized to arthroscopic partial meniscectomy compared to patients randomized to physical therapy with optional delayed arthroscopic partial meniscectomy. Patients randomized to arthroscopic partial meniscectomy without cartilage defects on baseline had a higher incidence of new cartilage defects at 24 months compared to those randomized to physical therapy. In conjunction with the results of *chapter 4 and 5*, these findings suggest that at group level, arthroscopic partial meniscectomy is not superior in terms of clinical, cost-effectiveness and knee degeneration outcomes, when compared to physical therapy with optional delayed arthroscopic partial meniscectomy. This represents a novel insight into the management of young patients with isolated traumatic meniscal tears.

DUTCH SUMMARY (NEDERLANDSE SAMENVATTING)

Een traumatisch knieletsel komt vaak voor bij jonge actieve mensen. Veelvoorkomende letsels zijn een ruptuur van de voorste kruisband en een traumatische meniscusscheur.
Bij de behandeling van voorste kruisbandrupturen wordt wereldwijd vaak gekozen voor een operatieve reconstructie van de voorste kruisband. Tot nu toe zijn er twee gerandomiseerde klinische onderzoeken gepubliceerd die een operatieve reconstructie kort na het ontstaan van het letsel hebben vergeleken met een niet-operatieve (conservatieve) behandelstrategie. Beide onderzoeken hebben tot de conclusie geleid dat een deel van de patiënten met een ruptuur van de voorste kruisband ook een goed klinisch resultaat kan behalen met oefentherapie onder begeleiding van een fysiotherapeut zonder operatieve reconstructie. Bij een deel van de patiënten was de fysiotherapie behandeling niet succesvol en zij ondergingen later alsnog een voorste kruisbandreconstructie. Een veel benoemd risico van conservatief of uitgesteld operatief behandelen van voorste kruisbandrupturen is dat de resterende instabiliteit van het kniegewricht een aanvullend letsel zou kunnen veroorzaken, zoals een meniscusscheur. In dit proefschrift wordt ingegaan op waarom oefentherapie bij sommige patiënten niet afdoende is en of het niet, of uitgesteld opereren bij een voorste kruisbandruptuur inderdaad leidt tot meer meniscusletsels. We hebben hiervoor gebruik gemaakt van data van de COMPARE studie, één van de twee gerandomiseerde klinische onderzoeken bij patiënten met een voorste kruisbandruptuur. In de COMPARE studie werden 167 patiënten geïncludeerd, waarvan 85 werden gerandomiseerd voor directe voorste kruisbandreconstructie en 82 voor fysiotherapie met de mogelijkheid tot een uitgestelde voorste kruisbandreconstructie. Van deze 82 patiënten ondergingen 41 patiënten een uitgestelde voorste kruisbandreconstructie tijdens de studieperiode van twee jaar. *Hoofdstuk 2* beschrijft waarom, wanneer en welke patiënten uiteindelijk een operatie ondergingen. Hiervoor werden scores uit vragenlijsten voor de operatie verzameld: de International Knee Documentation Committee (IKDC), mate van ervaren pijnscore en mate van ervaren instabiliteit. De IKDC meet de perceptie van patiënten over hun symptomen, kniefunctie en vermogen om aan sportactiviteiten deel te nemen, met 100 als beste score en 0 als laagste score. Van de 41 uitgestelde voorste kruisbandreconstructies vond de meerderheid plaats tussen drie en zes maanden na inclusie, met als meest genoemde reden daarvoor instabiliteit van de aangedane knie. Het merendeel van de patiënten rapporteerde daarnaast in de verschillende vragenlijsten een IKDC score lager dan 60, een pijnscore boven de 3 en ervaren instabiliteit van de knie. Tijdens follow-up hadden patiënten die een uitgestelde reconstructie ondergingen een lagere IKDC score en een hogere pijnscore vergeleken met patiënten die wel succesvol waren met fysiotherapie, gecorrigeerd voor geslacht, leeftijd en BMI. Patiënten die een uitgestelde voorste kruisbandreconstructie ondergingen waren significant jonger dan de patiënten die geen operatie ondergingen en hadden voor hun voorste kruisbandruptuur

een hoger activiteitenniveau dan patiënten die succesvol waren met fysiotherapie. Deze studie geeft meer inzicht in waarom, wanneer en welke patiënten met een voorste kruisbandruptuur niet slagen met fysiotherapie.

In *hoofdstuk 3* wordt met data van de COMPARE studie onderzocht of een niet-operatieve behandeling van voorste kruisbandrupturen leidt tot meer meniscusoperaties vergeleken met een direct operatieve behandeling. Het aantal meniscusingrepen werd vergeleken tussen de patiënten die waren gerandomiseerd voor directe voorste kruisbandreconstructie (n=85) of voor fysiotherapie met de mogelijkheid tot een uitgestelde voorste kruisbandreconstructie (n=82). Het aantal meniscusingrepen tijdens de tweejarige follow-up periode werd vergeleken tussen beide groepen en gecorrigeerd voor geslacht, BMI, leeftijd en behandelend orthopedisch chirurg. Op baseline had 41% van alle patiënten (69/167) een meniscusscheur op de MRI. Van de 85 patiënten gerandomiseerd voor een directe voorste kruisbandreconstructie ondergingen 25 patiënten (29%) een meniscusingreep tijdens follow-up, vergeleken met 17 van de 82 patiënten (21%) gerandomiseerd voor fysiotherapie met de mogelijkheid tot een uitgestelde reconstructie (risico ratio 0,67 met 95% betrouwbaarheidsinterval 0,40 tot 1,12 en p-waarde 0,12). Van de patiënten die een directe of uitgestelde voorste kruisbandreconstructie ondergingen had 5% een extra meniscusingreep na de voorste kruisbandreconstructie. Bij patiënten die geen reconstructie ondergingen had 10% (n=4) een meniscusingreep tijdens de follow-up periode. Op basis van deze studie concluderen we dat starten met een niet-operatieve behandeling bij voorste kruisbandrupturen niet leidt tot meer meniscusingrepen vergeleken met een direct operatieve behandeling.

Traumatische meniscusscheuren bij jonge patiënten worden vrijwel altijd operatief behandeld. Er is tot op heden geen goed bewijs dat een meniscusoperatie beter is dan een niet-operatieve behandelstrategie. Daarom werd een multicenter gerandomiseerde studie opgezet, de STARR studie, waarbij patiënten tussen de 18 en 45 jaar oud met een geïsoleerde traumatische meniscusscheur, zonder artrose van het kniegewricht, werden geïncludeerd. Deze patiënten werden gerandomiseerd tussen een operatieve behandeling (arthroscopische partiële meniscectomie) of een conservatieve behandelstrategie (minimaal drie maanden fysiotherapie met de mogelijkheid tot een uitgestelde partiële meniscectomie bij persisterende klachten). Alle patiënten werden gedurende een periode van 24 maanden gevolgd. *Hoofdstuk 4* beschrijft de klinische resultaten van de STARR studie. De primaire uitkomstmaat was de IKDC score na 24 maanden. Tussen 2014 en 2018 werden 100 patiënten geïncludeerd met een gemiddelde leeftijd van 35 jaar. Hiervan werden 49 patiënten gerandomiseerd voor arthroscopische partiële meniscectomie en 51 voor fysiotherapie. In de fysiotherapiegroep ondergingen 21 patiënten (41%) een uitgestelde partiële meniscectomie tijdens de follow-up periode. In beide groepen ging de IKDC score tijdens follow-up klinisch relevant vooruit ten opzichte van de baseline scores. Na 24 maanden was de gemiddelde IKDC score 78 (95% betrouwbaarheidsinterval 71 tot 84) in zowel de arthroscopische partiële meniscectomie groep als de fysiotherapie groep met een verschil tussen beide groepen van 0,1 (95% betrouwbaarheidsinterval -7,6 tot 7,7). Op basis van deze resultaten concluderen we dat in de STARR studie bij jonge patiënten met een geïsoleerde traumatische meniscusscheur na 24 maanden follow-up arthroscopische partiële meniscectomie niet superieur is aan fysiotherapie met de mogelijkheid tot een uitgestelde partiële meniscectomie.

Omdat in de overweging welke behandeling het beste is niet alleen effectiviteit een rol speelt, maar ook kosten die er mee samenhangen, werd er een kosteneffectiviteitsanalyse gedaan van de STARR studie. Hierbij werd de kosteneffectiviteit van arthroscopische partiële meniscectomie vergeleken met fysiotherapie. *Hoofdstuk 5* beschrijft de resultaten van deze analyse. Kostenutiliteit werd berekend als kosten per gewonnen kwaliteitsgewogen levensjaar ('quality adjusted life year'; QALY) van arthroscopische partiële meniscectomie vergeleken met fysiotherapie met de mogelijkheid tot een uitgestelde partiële meniscectomie over een periode van 24 maanden. Berekeningen werden uitgevoerd vanuit een medisch en maatschappelijk perspectief. Gedurende 24 maanden hadden patiënten in de meniscectomie groep gemiddeld een 0,005 QALY lagere kwaliteit van leven (95% betrouwbaarheidsinterval -0,13 tot 0,14). De kostenutiliteitsratio was €-160.000/QALY vanuit het medisch perspectief en €-223.372/QALY vanuit het maatschappelijk perspectief, wijzend op meer kosten bij arthroscopische partiële meniscectomie, zonder dat dit gezondheidswinst oplevert. Dit onderzoek concludeert dat arthroscopische partiële meniscectomie waarschijnlijk niet kosteneffectief is bij de behandeling van jonge patiënten met een geïsoleerde traumatische meniscusscheur.

Hoofdstuk 6 beschrijft posttraumatische en aan artrose gerelateerde afwijkingen op MRI bij de patiënten met een traumatische meniscusscheur. Om dit te onderzoeken hebben we alle baseline MRI's van de patiënten van de STARR trial en van gezonde controlepatiënten gescoord met de MRI Osteoarthritis Knee Score (MOAKS). We hebben beenmergoedeem, kraakbeendefecten en osteofyten beschreven. Op baseline hadden patiënten vaker één of meer gebieden met beenmergoedeem vergeleken met de controles. Gebieden met ernstig beenmergoedeem waren vrijwel uitsluitend aanwezig bij patiënten, dit gold ook voor kraakbeendefecten. Osteofyten kwamen bij patiënten en controles even vaak voor. De helft van de patiënten had een gebied met beenmergoedeem in hetzelfde compartiment van het kniegewricht als hun meniscusscheur. In deze studie vonden we bij patiënten met een traumatische meniscusscheur meer gebieden met ernstig beenmergoedeem en kraakbeendefecten vergeleken met controles.

Naast de resultaten van de klinische en kosteneffectiviteit gerelateerde uitkomstmaten van de STARR studie, hebben we ook onderzocht wat het effect is van de twee verschillende behandelingen op degeneratie van het kniegewricht. *Hoofdstuk 7* vergelijkt degeneratieve veranderingen op MRI na 24 maanden tussen arthroscopische partiële meniscectomie en fysiotherapie met de mogelijkheid tot een uitgestelde partiële meniscectomie. De MRI's van baseline en 24 maanden werden gescoord met de MOAKS. De uitkomst was de progressie van beenmergoedeem en kraakbeendefecten na 24 maanden. Na 24 maanden vonden we bij de arthroscopische partiële meniscectomie groep vaker progressie van beenmergoedeem en kraakbeendefecten vergeleken met de fysiotherapie groep. Ook hadden patiënten gerandomiseerd voor arthroscopische partiële meniscectomie zonder een kraakbeendefect op baseline, vaker alsnog een kraakbeendefect na 24 maanden dan patiënten gerandomiseerd voor fysiotherapie. Samen met de resultaten van *hoofdstuk 4 en 5* impliceren deze bevindingen dat op groepsniveau arthroscopische partiële meniscectomie zowel klinisch, als qua kosteneffectiviteit als qua effect op degeneratie van het kniegewricht niet beter is dan behandeling met fysiotherapie met de mogelijkheid tot een uitgestelde partiële meniscectomie. Dit is een nieuw inzicht in de behandeling van patiënten met geïsoleerde traumatische meniscusscheuren, waarover tot op heden nog weinig literatuur beschikbaar was.

LIST OF PUBLICATIONS

van der Graaff SJA, Oei EHG, Reijman M, Steenbekkers L, van Middelkoop M, van der Heijden RA, Meuffels DE; STARR Study Group. Post-traumatic and OA-related lesions in the knee at baseline and 2 years after traumatic meniscal injury: secondary analysis of a randomized controlled trial. Osteoarthritis Cartilage. 2024 Apr 2:S1063-4584(24)01132-4.

van der Graaff SJA, Reijman M, Meuffels DE, Koopmanschap MA; STARR Study Group; STARR Study Group; Eijgenraam SM, van Es EM, Hofstee DJ, Auw Yang KG, Noorduyn JCA, van Arkel ERA, van den Brand ICJB, Janssen RPA, Liu WY, Bierma-Zeinstra SMA. Cost-effectiveness of arthroscopic partial meniscectomy versus physical therapy for traumatic meniscal tears in patients aged under 45 years. Bone Joint J. 2023 Nov 1;105-B(11):1177-1183.

van der Graaff SJA, Reijman M, van Es EM, Bierma-Zeinstra SMA, Verhaar JAN, Meuffels DE. Meniscal procedures are not increased with delayed ACL reconstruction and rehabilitation: results from a randomised controlled trial. Br J Sports Med. 2023 Jan;57(2):78-82.

van der Graaff SJA, Eijgenraam SM, Meuffels DE, van Es EM, Verhaar JAN, Hofstee DJ, Auw Yang KG, Noorduyn JCA, van Arkel ERA, van den Brand ICJB, Janssen RPA, Liu WY, Bierma-Zeinstra SMA, Reijman M. Arthroscopic partial meniscectomy versus physical therapy for traumatic meniscal tears in a young study population: a randomised controlled trial. Br J Sports Med. 2022 Jun 8;56(15):870–6.

van der Graaff SJA, Meuffels DE, Bierma-Zeinstra SMA, van Es EM, Verhaar JAN, Eggerding V, Reijman M. Why, when, and in which patients nonoperative treatment of anterior cruciate ligament injury fails: an exploratory analysis of the COMPARE trial. Am J Sports Med. 2022 Mar;50(3):645-651.

PHD PORTFOLIO

Name PhD student:	**PhD period:**	**Promotor:**
S.J.A. van der Graaff	01-03-2020 – 31-12-2023	Prof. dr. J.A.N. Verhaar
Erasmus MC Department:		**Copromotors:**
Orthopaedics and Sports Medicine		Dr. M. Reijman
		Dr. D.E. Meuffels

	Date:	Workload (ECTS):
General courses		
• BROK (Basic course Rules and Organisation for Clinical researchers)	05-2020	1,5
• Systematic literature retrieval in PubMed Part 1&2	05-2020	0,8
• Biomedical English Writing	09-2020	2,0
• Biostatistical Methods I: Basic Principles (CC02)	10-2020	5,7
• Scientific Integrity	11-2020	0,3
Seminars and workshops		
• Presentation workshop part 1&2	07-2020 – 09-2020	0,4
• Erasmus MC PhD day 2021	19-03-2021	0,2
• ROGO day	10-11-2021	
Oral presentations		
• NOV voorjaarscongres 2021 *Meniscusletsels nemen niet toe bij uitgestelde VKB reconstructie en fysiotherapie: resultaten van een gerandomiseerd klinisch onderzoek*	05-2021	1,0
• ACE Bone & Joint meeting *Meniscal procedures are not increased with delayed ACL reconstruction and rehabilitation: results from a randomised controlled trial*	26-07-2021	0,5
• Physio Global live podcast *The subtle art of ACL rupture rehabilitation: early surgical reconstruction vs. rehabilitation with elective delayed reconstruction*	16-10-2021	1,0
• ISAKOS Global 2021 *- Why, when and who fails non-operative treatment of anterior cruciate ligament injury – an exploratory analysis of the COMPARE trial* *- Meniscal procedures are not increased with delayed ACL reconstruction and rehabilitation: results from a randomized controlled trial*	11-2021	2,0

Continued.

	Date:	Workload (ECTS):
• ESSKA Congress 2022 Paris *Meniscal procedures are not increased with delayed ACL reconstruction and rehabilitation: results from a randomized controlled trial*	04-2022	1,0
• NVA Jaarcongres 2022 *Arthroscopic Partial Meniscectomy versus Physical Therapy for Traumatic Meniscal Tears in a Young Study Population: a Randomised Controlled Trial*	24-06-2022	1,0
• Sportmedisch Wetenschappelijk Jaarcongres 2022 *Arthroscopic Partial Meniscectomy versus Physical Therapy for Traumatic Meniscal Tears in a Young Study Population: a Randomised Controlled Trial*	06-2022	1,0
• NOV Najaarscongres 2022 *Arthroscopic Partial Meniscectomy versus Physical Therapy for Traumatic Meniscal Tears in a Young Study Population: a Randomised Controlled Trial*	10-2022	1,0
• Soup and science meeting *MRI findings in traumatic meniscal tears - MRI data from the STARR trial*	24-11-2022	1,0
• NOV Jaarcongres 2023 *Degeneratieve veranderingen op MRI 2 jaar na een traumatische meniscusscheur: arthroscopische partiële meniscectomie versus fysiotherapie*	05-2023	1,0
Awards		
• Dr. Eikelaar Award 2022	06-2022	
• 'Beste Vrije Voordracht' Sportmedisch Wetenschappelijk Jaarcongres 2022	06-2022	
• 'Best national paper' NOV *Degeneratieve veranderingen op MRI 2 jaar na een traumatische meniscusscheur: arthroscopische partiële meniscectomie versus fysiotherapie*	12-2023	
Teaching		
• Teaching students of Department of Orthopaedics and Sports Medicine during their master research	06-2021 – 07-2021	1,0
Supervising master students		
• Supervising master student Lars Steenbekkers during scoring of MRIs of the STARR trial	10-2020 – 04-2021	5,0
• Supervising master student Sakis Terzidis during performing a systematic review	05-2020 – 03-2023	5,0
Total		**32,4 ECTS**

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CURRICULUM VITAE

Sabine van der Graaff werd geboren op 30 januari 1995 te Rossum, Gelderland. Zij groeide op in Dordrecht en behaalde in 2012 haar diploma aan het Johan de Witt Gymnasium. Aansluitend startte zij met de studie Geneeskunde aan de Erasmus Universiteit Rotterdam. Tijdens haar studie heeft ze haar masteronderzoek gedaan aan de Harvard School of Dental Medicine in Boston, Verenigde Staten. Zij volgde haar keuze- en oudste coschappen bij de afdeling Orthopedie van het Erasmus MC en Reinier de Graaf. In 2019 ontving zij haar artsendiploma.

Aansluitend aan haar studie startte zij met haar promotieonderzoek op de afdeling Orthopedie en Sportgeneeskunde van het Erasmus MC. Na anderhalf jaar fulltime onderzoek doen werkte zij als arts-assistent niet in opleiding achtereenvolgens bij de afdeling Chirurgie van het Franciscus Gasthuis en Orthopedie van het Maasstad Ziekenhuis. In maart 2023 besloot zij zich te verdiepen in de Revalidatiegeneeskunde, met een plek als arts-assistent niet in opleiding bij Rijndam Revalidatie. Datzelfde jaar werd zij aangenomen voor de opleiding tot revalidatiearts. In januari 2024 is zij gestart als arts-assistent in opleiding tot revalidatiearts bij Rijndam Revalidatie onder begeleiding van drs. K. Nieuwenhuis en dr. M. van der Werf.

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