IDENTIFICATION OF EARLY DEGENERATIVE CHANGES IN THE KNEE AFTER ANTERIOR CRUCIATE LIGAMENT RUPTURE

Belle L. van Meer

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CHAPTER 1

General Introduction

OSTEOARTHRITIS

Osteoarthritis (OA) is a common disease of the musculoskeletal system. In the Netherlands approximately 1.2 million people suffer from OA.[1] OA can arise in all synovial joints, but knee, hand and hip are most often affected.[2,3] The incidence rate of OA is growing after the age of 50 years.[4] Besides, prevalence of OA is increasing because of aging of the population and gaining prevalence of obesity.[1,5] Symptomatic knee OA is most prevalent, almost twice compared to hip OA. Based on registrations in Dutch health care, the prevalence for symptomatic knee OA is estimated to be 44 per 1000 women and 28 per 1000 men.[1]

OA is generally regarded as a degenerative disease of the whole joint with involvement of all tissues: cartilage, (subchondral) bone, synovial fluid, ligaments, and surrounding muscles.[6,7] Clinical signs of knee OA are joint pain, stiffness and limited joint function.[8] These symptoms limit daily activities and influence quality of life of patients negatively.[3,9] Knee OA is a multifactorial disease,[2] and well-known risk factors are obesity, female sex, older age and previous knee injury.[10-13] The meta-analysis of Blagojevic et al. showed that previous knee injury the strongest risk factor was for onset of knee OA.[11] In the current thesis the main focus is which (degenerative) changes develop after a common knee injury: anterior cruciate ligament (ACL) rupture.

Curative treatment options do not exist for OA. Up to now no disease modifying OA drugs has proven to be effective.[14] Conservative treatment options for knee OA, such as exercise, weight reduction in overweight or obese patients, anti-inflammatory drugs and intra-articular injections mainly aim symptomatic relief. In addition, if relief of symptoms fails after conservative treatment, osteotomy, unicompartmental arthroplasty and, for end-stage disease, total knee arthroplasty could be considered.[15-17]

Knee OA is one of the leading causes for global disability with high burden concerning both individual and socioeconomic consequences.[18,19] The burden of OA could be divided into direct costs (medical consumption), indirect costs (reduced employment, reduced productivity, absenteeism) and intangible costs (pain, reduced social participation, activity limitation, decreased quality of live).[19]

ANTERIOR CRUCIATE LIGAMENT RUPTURE

ACL rupture is a common sport related injury, with an annual incidence of 5 to 8 per 10,000 persons in the general population.[20-22] The annual incidence rate for ACL injuries in amateur athletes is higher (3 to 162 per 10,000 persons) compared to the general population. In professional sports the annual incidence rate is much higher: 15 to 367 per 10,000 persons.[20] These data were extracted from studies from different

countries. The exact incidence rate in the Netherlands is unknown. The number of ACL reconstructions is estimated at 6000 per year in the Netherlands.[23] Women have a three to five times greater risk of ACL rupture then men.[24]

Isolated ACL rupture is uncommon, associated injuries often coexist. Reported incidence of concomitant meniscal lesions varies between 15 to 65%, lateral meniscal lesion is more common than medial meniscal lesion.[25-27] In chronic ACL-deficient knees incidence of meniscal injuries is higher.[24] Incidence of simultaneous cartilage injuries is reported up to 46%.[26,28-31] Traumatic bone marrow lesions (BML), also named "bone bruises", have been reported to occur in 80% or more in patients with an acute ACL rupture.[32-34] BML's represent a footprint of the ACL injury mechanism; frequently located in the lateral femur condyle and the posterolateral tibia plateau.[35] Reported resolution of post-traumatic BMLs varied between 6 months and more than 2 years.[36-39] Reports of associated medial collateral ligament injury range from 5 to 22%.[40,41] These percentages are dependent of time of assessment after injury and used method, e.g. MRI examination versus physical examination (under anaesthesia). Rupture of posterolateral and lateral ligaments is not commonly associated with ACL injury, but for successful ACL reconstruction it is important that posterolateral injuries are recognized and treated.[25]

The ACL is an intra-articular ligament with limited healing capacity. Unlike the medial collateral ligament, there is no formation of functional scar tissue or increased histologic blood flow during recovery. It appears that, after ACL rupture, a layer of synovial tissue surrounds the ruptured ends; cells in this synovial tissue may retract tissue and limit healing.[42-44] However, some radiographic studies showed (partial) ACL recovery on MRI with different outcomes of relationship with improvement of clinical stability.[45-51]

Current treatment options are non-operative treatment with rehabilitation or surgical reconstruction of the ACL. The recommendation of the national ACL guideline in the Netherlands is as follows: if initial knee instability exists, operative treatment is chosen; otherwise, non-operative treatment is indicated.[52] However, the decision between non-operative and operative treatment can be complex, and is also influenced by different variables, for example, the patient's activity, willingness to modify activities and additional injuries. Worldwide it is debated which treatment option is the best for short- and long-term outcome. Both treatment options are associated with comparable short-, mid- and long-term results regarding function and OA.[53-56]

The impact of an ACL injury is tremendous: firstly, the rehabilitation period is long and intensively; secondly, after mid-term follow-up patients report poorer knee related quality of live compared with population norms.[57] Finally, as stated before patients after an ACL injury have an increased risk of development of knee OA. Because ACL

injury is common in the young and active population, these patients will probably develop OA at a young age.[24]

ANTERIOR CRUCIATE LIGAMENT RUPTURE AND OSTEOARTHRITIS

As above described, OA is a well-known, devastating long-term consequence of ACL rupture, with prevalence of 10-90% at 10 to 20 years post-injury. Reporting a mean rate is difficult because of the great variability of the results.[24,58] A systematic review showed that high rated studies regarding methodology, reported lower prevalences of OA after minimal 10 years follow-up: 0-13% in patients with an isolated ACL rupture. In contrast, the risk of OA in patients with combined injuries was 21-48%.[59] A recent meta-analysis of 16 studies with a minimum of 10 years follow-up after ACL reconstruction found also a lower rate of OA (28%) and confirmed that the risk of developing OA after ACL reconstruction increased when associated meniscectomy was performed.[60]

Post-traumatic OA patients are typically young and especially in the young patient with OA the burden of OA will be high because of the long-lasting medical consumption and influence on employment. For example, direct and indirect costs attributable to OA in active subjects in a Belgian study were 44.5 and 64.5 euros respectively per OA patient-month.[61] For the young patients at risk for OA development it would be important to have possibilities to intervene early in the degenerative process and to prevent or postpone total knee arthroplasty, because of the risk of revision.[62] However, not all patients will develop OA after an ACL rupture.[59,60] Therefore, it is important to recognize the ACL-deficient patient at risk for degenerative changes, or to recognize OA changes after the injury early in the developmental process.

We do not know exactly what is determinative for the development of knee OA after ACL rupture. There are several hypotheses of this process for the development of knee OA after ACL rupture. Firstly, associated initial joint damage with ACL injury, like BMLs, cartilage and meniscal injury may play a role in initiating OA.[63]

Secondly, it seems that development and progression of OA are influenced by changes in bone, based on increased bone metabolism in OA joints.[64-67] Previous findings of animal and clinical studies suggest a biphasic process of BMD changes in OA: a reduction in BMD early on followed by an increase during more advanced phase.[68-74] It seems that in the early phase thinning and increased porosity of the subchondral plate caused by increased osteoclast activity influence the biomechanical function of the osteochondral junction and has an influence on the underlying cartilage. In the more advanced phase of OA development osteoblast activity is increased, resulting in production of sclerotic bone and osteophyte formation.[73-75] Several studies have reported

a decrease of BMD after an ACL rupture, however these BMD levels were measured at different locations: patella, distal femur, proximal tibia, several hip sites, lumbar spine and calcaneus and the sample sizes of the studies were small.[76]

Thirdly, another assumption for development of knee OA after ACL injury is increased instability resulting in changes of knee loading and altered knee kinematics.[77] Furthermore, these factors may influence the occurrence of additional lesions, as meniscal and chondral injuries,[78-80] which may have an influence on the development of OA.[24]

Finally, inflammation-related factors induced after ACL rupture may affect cartilage and bone and may play a role in the initiation of the OA process.[81] Furthermore, intra-articular bleeding, which is commonly present after ACL trauma, seems to influence the inflammatory response and subsequent cartilage damage in the joint.[82]

To identify the early process of OA development following ACL injury, it is important to visualize all minor changes in the knee, which could be early OA features. In clinical practice, reported symptoms and conventional radiography is mainly used to diagnose and monitor OA. However, radiography can only detect osseous changes and joint space narrowing, which are indirect measures of cartilage deterioration and meniscus integrity. Currently, in OA research Magnetic Resonance Imaging (MRI) has become an important tool for detection of early degenerative changes, because of its capability to visualize all structures in the knee joint. Another advantage of using MRI is the capability of showing structural changes in the knee earlier than on radiography or presence of clinical OA complaints.[83-85] Semi-quantitative scoring methods have shown to be reliable and sensitive for detecting structural changes using conventional MRI acquisitions.[86]

Early identification of the process of ACL rupture leading to OA may aid in preventing the onset or progression of OA. So, we have to know which factors are related to early degenerative changes for development of early interventions such as disease-modifying therapeutics targeting tissues in the knee joint and biomechanical interventions. Furthermore, knowledge of these risk factors may lead to identification of high-risk groups. Besides, assessment of early degenerative changes can be used as intermediate outcome for evaluating the effect of interventions after ACL rupture resulting in shorter follow-up of longitudinal studies.

KNEE OSTEOARTHRITIS ANTERIOR CRUCIATE LIGAMENT LESION (KNALL) STUDY

To identify early degenerative changes following ACL rupture a prospective observational study was designed: the KNALL study. ACL rupture had to be diagnosed by physical examination and MRI. Patients were treated non-operatively or operatively independent of the study. Because we are interested in early degenerative changes inclusion criteria were, baseline measurements within 6 months after initial ACL trauma and age between 18 and 45 years. Patients with previous ACL injury or meniscus or cartilage damage; those with previous surgery of involved knee; those with disabling co-morbidity and those with already osteoarthritic changes on knee radiograph (Kellgren & Lawrence grade > 0) were excluded. We also measured the contralateral knee, comprising as control group if this knee had no osteoarthritic changes on knee radiograph (Kellgren & Lawrence grade 0) and no previous knee injury or knee surgery. The included patients were evaluated at baseline, and after one and two years. At the three time points patients filled in several questionnaires (Knee injury and Osteoathritis Outcome Score, KOOS; International Knee Documentation Committee Subjective Knee Form, IKDC subjective, etc.), serum and urine were collected and a standardized physical examination, X-rays, MRI examination and BMD measurements of the knee were performed.

AIMS AND OUTLINE OF THIS THESIS

The general aim of this thesis is to identify which early (degenerative) changes occur after an ACL rupture and which determinants are related to these changes.

In **Chapter 2** we conducted a systematic review of the literature to summarize the evidence for determinants that influence the development of OA in patients with an ACL injury.

It is important to monitor patients with ACL ruptures over time to evaluate their recovery and to determine the effectiveness of different interventions during clinical studies. Monitoring patient's perception of the knee during daily living and sports activities can be done using self-administered questionnaires. Two frequently used questionnaires are the Knee injury and Osteoathritis Outcome Score (KOOS) and the International Knee Documentation Committee Subjective Knee Form (IKDC subjective). For follow-up and evaluating outcomes of patients with ACL injuries uniformity of the use of questionnaire is important. Therefore we evaluated in **Chapter 3** which questionnaire, KOOS or IKDC subjective, is most useful to evaluate patients with recent ACL ruptures or those within one year of an ACL reconstruction. Data was

used from the KNALL study and from a prospective randomized controlled trial that compared the results of computer-assisted ACL reconstruction with the conventional arthroscopic method.[87]

We were interested in the intrinsic capacity of the ACL to recover after rupture expressed in changes in laxity by physical examination and the possibility to represent recovery on MRI. In **Chapter 4** the aim was to determine whether ACL features on MRI are changed in patients two years after ACL rupture treated non-operatively, and to determine whether knee laxity, as assessed by physical examination, is improved. We also analysed the relationship between these two diagnostic modalities. The non-operatively treated patients of the KNALL population were included in this study.

The aim of **Chapter 5** was to investigate bone mineral density (BMD) changes in the knee following ACL rupture in the KNALL population. Because of the known BMD changes during the OA process, we were interested in the influence of ACL rupture on BMD after trauma and during follow-up.

The aim of **Chapter 6** was to assess which OA features are detectable in ACL-deficient knees, assessed with MRI using a semi-quantitative scoring method, and how these OA features progress during 5-year follow-up.

In **Chapter 7** we identified in the KNALL study early degenerative changes after ACL rupture as assessed on MRI after two-year follow-up and investigated which determinants were related to these changes.

Finally, in **Chapter 8** the main findings and limitations of the studies described in this thesis are summarized and discussed and implications for future research on prevention of knee OA after ACL rupture are described.

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CHAPTER 2

Which determinants predict tibiofemoral and patellofemoral osteoarthritis after anterior cruciate ligament injury? A systematic review

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ABSTRACT

Background: Anterior cruciate ligament (ACL) injury is an important risk factor for development of knee osteoarthritis (OA). To identify those ACL injured patients at increased risk for knee OA, it is necessary to understand risk factors for OA.
Aim: To summarise the evidence for determinants of (i) tibiofemoral OA and (ii) patellofemoral OA in ACL injured patients.
Methods: MEDLINE, Embase, Web of Science, CINAHL databases were searched up to 20 December 2013. Additionally, reference lists of eligible studies were manually and independently screened by two reviewers. 2348 studies were assessed for the following main inclusion criteria: ≥ 20 patients; ACL injured patients treated operatively or non-operatively; reporting OA as outcome; description of relationship between OA outcome and determinants; and a follow-up period ≥ 2 years. Two reviewers extracted the data, assessed the risk of bias and performed a best-evidence synthesis.
Results: Sixty-four publications were included and assessed for quality. Two studies were classified as low-risk of bias. Medial meniscal injury/ meniscectomy showed moderate evidence for influencing OA development (tibiofemoral OA and compartment unspecified). Lateral meniscal injury/ meniscectomy showed moderate evidence for no relationship (compartment unspecified), as did time between injury and reconstruction (tibiofemoral and patellofemoral OA).
Conclusion: Medial meniscal injury/ meniscectomy after ACL rupture increased the risk of OA development. In contrast, it seems that lateral meniscal injury/ meniscectomy has no relationship with OA development. Our results suggest that time between injury and reconstruction does not influence patellofemoral and tibiofemoral OA development. Many determinants showed conflicting and limited evidence and no determinant showed strong evidence.

INTRODUCTION

Anterior cruciate ligament (ACL) rupture is a common sports-related injury, with an annual incidence of approximately 5 per 10,000 persons in the general population.[1] Osteoarthritis (OA) is a well-known, long-term complication of ACL rupture, with a prevalence of 10-90% at 10 to 20 years post-injury.[2,3] It is important to identify the risk factors contributing to OA in patients with ACL rupture, because some risk factors may be modifiable as to prevent onset or early-stage progression of OA. At present, the only treatment options for OA are symptomatic relief, osteotomy, unicompartmental arthroplasty and, for end-stage disease, total knee arthroplasty. Early intervention is critical because post-traumatic OA patients are typically young and it is important to postpone total knee arthroplasty.[4]

Numerous studies have evaluated the long-term consequences of ACL rupture. These studies are heterogeneous with regard to methodology, including treatments used, inclusion of additional intra-articular injuries, reported OA outcomes, and descriptions of determinants (potential risk factors). Three previous systematic reviews of development of OA after ACL rupture were limited either because they considered OA only in the tibiofemoral compartment or because they focused on one type of treatment (ACL reconstruction). Oiestad et al.[5] conducted a systematic review of the prevalence of OA in the tibiofemoral joint occurring more than 10 years after ACL injury. They included studies that used ACL reconstruction techniques, which are no longer used (e.g., Leeds-Keio polyester ligament surgery or suturing of the ACL). Therefore, we did not include these techniques in this systematic review. To better evaluate newer and current techniques and rehabilitation methods, we included only studies which reported results based on current ACL reconstruction procedures. Magnussen et al.[6] reviewed patient factors affecting clinical and radiographic outcomes after ACL reconstruction in prospective studies with a 5-year minimum follow-up. Prospective study design was an inclusion criterion, so they missed the results of all retrospective studies. Claes et al.[7] reviewed the literature on long-term radiographic outcome after autologous ACL reconstruction; studies with a mean follow-up of less than 10 years were excluded. They investigated only one predictor, namely the relationship between meniscal status and OA development in the reconstructed knee. Currently, there is no consensus about operative or non-operative treatment for preventing OA, and degenerative changes can develop in all knee compartments.

Culvenor et al.[8] showed in their narrative literature review that patellofemoral OA after ACL reconstruction occurs as frequently as tibiofemoral OA. Different mechanisms, like inflammation, concomitant injuries to the patellofemoral articular cartilage,

meniscal injury, graft choice, and changes of knee biomechanics may play a role in the development of patellofemoral OA.[8]

The previous published reviews presented a part of the general question: which determinants influence the development of degenerative changes after an ACL rupture? This systematic review will fill the gaps of the previous reviews and supplement with recent published literature on both tibiofemoral and patellofemoral OA. We systematically reviewed the evidence for determinants of both (i) tibiofemoral osteoarthritis (OA) and (ii) patellofemoral OA in patients with an anterior cruciate ligament (ACL) injury treated operatively or non-operatively.

METHODS

The reporting in this systematic review was conducted according to the PRISMA statement.[9]

Data Sources and Searches

MEDLINE, Embase, Web of Science and CINAHL medical literature databases were searched up to 20 December 2013. Search terms included anterior cruciate ligament, synonyms for injury and synonyms for osteoarthritis. The full electronic search strategy for the MEDLINE database is presented in Table 1. Similar search strategies were used in Embase, Web of Science and CINAHL. Additionally, the reference lists of all eligible studies were manually screened.

Table 1. Search strategy for MEDLINE

(anterior cruciate*[tw] OR acl[tw])
AND
(rupture*[tw] OR tear*[tw] OR torn*[tw] OR lacerat*[tw] OR defici*[tw] OR injur*[tw] OR lesion*[tw] OR disrupt*[tw] OR trauma*[tw] OR reconstruct*[tw] OR repair*[tw])
AND
(osteoarthrit*[tw] OR osteo-arthrit*[tw] OR osteoarthro*[tw] OR osteo-arthro*[tw] OR arthrosis[tw] OR arthroses[tw] OR arthrot*[tw] OR gonarthro*[tw] OR degen*[tw]
NOT
(animals[mesh] NOT humans[mesh])

Study Selection

Two reviewers (BvM, MR) assessed the studies for the following inclusion criteria:

- The following study designs with at least 20 patients: randomised controlled trial, prospective follow-up study, matched case-control study and retrospective study;
- Subjects had to have an ACL injury consisting of:
  - Patients treated non-operatively

  or
  - Patients treated operatively; use of an arthroscopic or mini-arthrotomy technique and use of bone-patellar tendon-bone, hamstring tendon or allografts
- Written in English, German, Dutch, Spanish, French, Swedish, Danish or Norwegian;
- Full text available;
- Measured one of the following OA outcomes:
  - Clinical OA: according to a clinician, self-reported or American College of Rheumatology (ACR) criteria;[10] osteotomy, unilateral knee arthroplasty or total knee arthroplasty (indirect measures for clinical knee OA);
  - Radiographic OA;
  - OA findings on MRI;
  - OA findings during arthroscopy;
- The relationship between outcome and determinant, defined as potential risk factor, must have been described or data must be available to calculate the relationship;
- Determinant studied in ≥ 2 studies
- Determinant must be measured prior to OA outcome
- Follow-up period of at least 2 years.

Animal studies and reviews were excluded. Disagreements on inclusions were resolved by discussion, and if necessary a final decision was made by a third reviewer (JV).

Data Extraction and Risk of Bias Assessment

Two reviewers (WvE and BvM) extracted the study characteristics, follow-up times, determinants, outcomes, and the relationship between outcome and determinant.

The determinants were grouped into *patient characteristics (age, BMI, sex)*, *physical examination, activity level* and *intra-articular related factors*. Determinant *Laxity* consisted of results of a pivot shift test, Lachman test, KT 1000 arthrometer or description of "laxity". The location of injury of the intra-articular determinants: *chondral injury* and *meniscal injury/ meniscectomy* were presented when reported as such in the studies. For determining the influence of *Tunnel placement* on OA development, we used the assessment of tunnel position when a study evaluated both femoral and tibial tunnel position, and graft inclination. If studies had the same population and determinant, but different follow-up times, we presented the results of the study with the longest

follow-up time. When a determinant was measured in various ways and had different relationships with OA outcome in one study, all results were presented. For the analyses of the relationship between determinants and OA outcome the distinction between patellofemoral and tibiofemoral OA was made. If the studies reported their results for all compartments as one entity or the compartment was not reported, then the study was classified as OA outcome in which the compartment was unspecified. Because the included studies presented the relationship between determinant and OA outcome in various ways, we reported the presence of a "positive significant relationship" or "negative significant relationship" or "no significant relationship". For presentation of the results we distinguished the studies into two groups: 1) studies with inclusion of non-operatively treated patients and 2) studies with inclusion of both operatively and non-operatively or solely operatively treated patients.

We evaluated the selected studies on 12 aspects using modified questions of existing risk of bias assessment tools.[11-13] Our assessment tool contained questions about the aim of the study, description of inclusion and exclusion criteria, collection of data, validity and reliability of OA outcome measures, independent measure of determinants, valid and reliable measurement of determinants, follow-up period, loss to follow-up, and use of adequate statistical analyses. Four reviewers independently assessed the quality of the included studies. Disagreements were resolved by discussion. Studies were classified as low-risk of bias when they scored "adequate" on all the following topics: the authors reported inclusion of consecutive patients; there was unbiased assessment of the study outcome and determinants; the determinant measures were used accurately (valid and reliable); if there was a loss to follow-up less than 20% and there was a description of the reasons, and if there was correction for confounding. The assessment tool used is given in Appendix Table 1.

Data Synthesis and Analysis

Because the studies were considered clinically heterogeneous with regard to the outcome measures and determinants studied, it was not possible to pool the data for statistical analysis, and therefore we performed "a best-evidence synthesis".[14,15] With the use of the system developed by van Tulder et al,[15] the following ranking of levels of evidence was formulated: 1) Strong evidence is provided by 2 or more studies with low-risk of bias and by generally consistent findings in all studies (≥ 75% of the studies reported consistent findings). 2) Moderate evidence is provided by 1 low-risk of bias study and 2 or more high-risk of bias studies and by generally consistent findings in all studies (≥ 75%). 3) Limited evidence is provided by 1 or more high-risk of bias studies or 1 low-risk of bias study and by generally consistent findings (≥ 75%). 4) Conflicting

evidence is provided by conflicting findings (< 75% of the studies reported consistent findings). 5) No evidence is provided when no studies could be found.[16,17]

RESULTS

Identification and selection of the literature

The search resulted in 2348 studies, for which all abstracts were reviewed. After screening of the abstracts, 157 were identified as possibly relevant, and full texts were retrieved. After review of the full texts, 56 met all the inclusion criteria (Figure 1). There were no disagreements on inclusions. The references of all 56 studies were reviewed and 8 additional studies meeting the inclusion criteria were identified. Thus, 64 studies in total were included in this systematic review.

Description of the included studies

The characteristics of the included studies are presented in Appendix Table 2. The studies had the following designs: randomised controlled trial (n = 12),[18-29] prospective follow-up study (n = 22),[30-51] matched case-control study (n = 2),[52,53] and retrospective study (n = 28)[54-81]. The number of patients available for follow-up measurement in the studies ranged between 30 and 780. In 62 studies the OA outcome was determined with radiographs and in 2 studies by MRI assessment[28,47]. Only 2 studies[43,70] reported both radiological OA and clinical OA as outcomes. Therefore, the findings of this systematic review address the influence of radiological OA. In 47 studies (4956 patients) the treatment strategy was ACL reconstruction, in 4 studies[22,64,71,76] (273 patients) non-operative treatment, and in 13 studies[19,30,31,40,41,47,53,65,70,72,77,79,80] (1169 patients) both reconstruction and non-operative treatment. The mean follow-up time varied between 3.9 and 20 years.

Risk of bias assessment

Two studies[35,56] were classified as "low-risk of bias". Overview of quality assessment score of the included studies is presented in Appendix Table 3. The main aim of the two low-risk of bias studies was to investigate risk factors for development of knee OA after ACL reconstruction. In these studies the number of patients used for analyses was > 50; Ahn et al. had a sample size of more than one hundred patients (n=117). Janssen et al. used only hamstring tendon grafts and Ahn et al. bone-patellar tendon-bone grafts.

Influence of determinants in non-operatively treated patients

Four studies[22,64,71,76] included solely non-operatively treated patients. Limited evidence was found for a positive relationship between *meniscectomy* and development

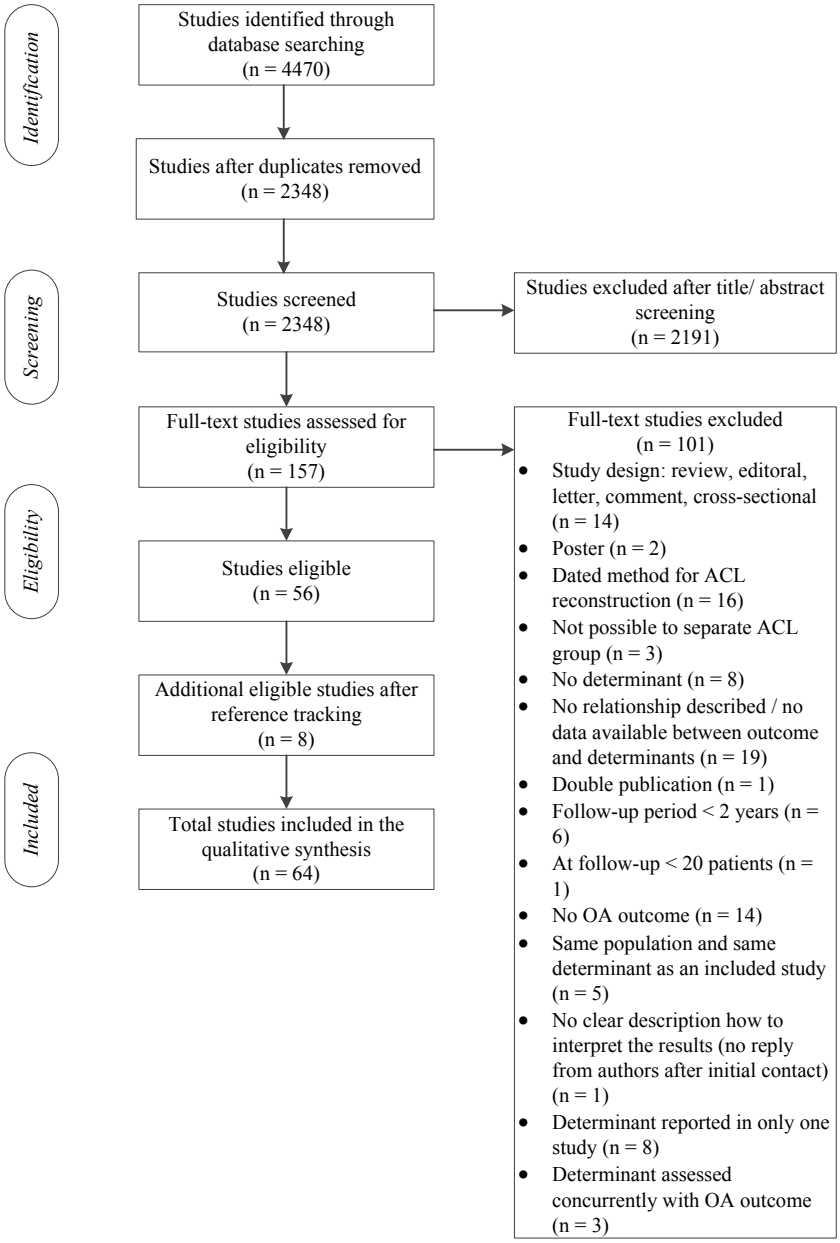

Figure 1. Study selection
Abbreviations: ACL, anterior cruciate ligament; OA, osteoarthritis

of knee OA in chronic ACL-deficient knees. Determinants *age, body mass index* and *sex* were excluded, because they were studied in only one study. Influence of *laxity* on OA development could not be presented because the laxity was measured concurrently with the OA outcome.

Influence of determinants in both operatively and non-operatively or solely operatively treated patients

Patient characteristics (table 2, 3 and 4)
Conflicting evidence was found for the influence of *age* on OA outcome in all compartments. For the influence of *body mass index* on OA outcome in the tibiofemoral compartment and compartment unspecified conflicting evidence was found after ACL rupture. Limited evidence for no relationship was found for OA development in the patellofemoral compartment after ACL rupture. Nine studies evaluated the relationship between *sex* and OA development after ACL rupture. For development of tibiofemoral OA 3 high-risk of bias studies[43,60,66] showed conflicting evidence. Moderate evidence was found for no relationship between male sex and OA development in compartment unspecified.[25,35,67,68,75,79]

Physical examination (table 4)
One low-risk of bias[35] and two high-risk of bias[34,45] studies showed no relationship between *laxity* and development of OA in compartment unspecified. Thus, there is moderate evidence for no relationship between laxity and OA development.[34,35,45] Moderate evidence was also found for no relationship between *range of motion* and OA development in compartment unspecified.[34,35,45,50] *Performance of single-legged hop test* was evaluated in 3 studies[34,35,45] and showed conflicting evidence.

Activity level (table 4)
One low-risk[35] and one high-risk[68] of bias study found no significant relationship between *activity level before reconstruction* and OA development (compartment unspecified).

Intra-articular related factors (table 2, 3 and 4)
Two high-risk of bias studies[44,63] investigating *additional injuries in general* showed conflicting evidence.

One high-risk of bias study[68] evaluated patellar, medial and lateral *chondral injury* after ACL rupture and their influence on OA development in compartment unspecified. Medial and patellar chondral injury showed a positive significant relationship with

Table 2. Influence of determinants on tibiofemoral radiological OA outcome in operatively and operatively/ non-operatively treated cohorts

Group	Determinant	n studies	Significant relationship LR / HR: n studies	No significant relationship LR / HR: n studies	Best Evidence Synthesis	Comments
Patient characteristics	Older age	6	Positive relationship: HR: 2 [43,66]	LR: 1 [56] HR: 3 [37,40,60]	Conflicting evidence	
	Higher BMI	4	Positive relationship: LR: 1 [56]* HR: 1 [66]	HR: 2 [40,43]	Conflicting evidence	* Ahn et al. [56]: lateral OA
	Male sex	3	Positive relationship: HR: 1 [43]	HR: 2 [60,66]	Conflicting evidence	
Intra-articular related factors	Additional injury	2	Positive relationship: HR: 1 [44]	HR: 1 [63]	Conflicting evidence	
	Chondral injury	3	Positive relationship: HR: 2 [37,60]	HR: 1 [66]	Conflicting evidence	
	Meniscal injury/ meniscectomy	11	Positive relationship: Medial meniscal injury/ meniscectomy: LR: 1 [56] HR: 2 [20,57]	Medial meniscal injury/ meniscectomy: None	Medial meniscal injury/ meniscectomy: Moderate evidence positive relationship	
			Lateral meniscal injury/ meniscectomy: HR: 1 [57]	Lateral meniscal injury/ meniscectomy: LR: 1 [56] HR: 1 [20]	Lateral meniscal injury/ meniscectomy: Conflicting evidence	
			Location not reported: HR: 6 [37,40,60,69,80,81]	Location not reported: HR: 2 [48,66]	Location not reported: Limited evidence positive relationship	

Table 2. Influence of determinants on tibiofemoral radiological OA outcome in operatively and operatively/ non-operatively treated cohorts (continued)

Group	Determinant	n studies	Significant relationship LR / HR: n studies	No significant relationship LR / HR: n studies	Best Evidence Synthesis	Comments
	Longer time between injury and reconstruction	6	Positive relationship HR: 1 [61]	LR: 1 [56] HR: 4 [37,43,60,66]	Moderate evidence for no relationship	
	ACL reconstruction versus non-operative treatment	7	Positive relationship HR: 2 [31,40] Negative relationship: HR: 1 [47]	HR: 4 [19,53,70,80]	Conflicting evidence	
	Graft type BPTB versus HT	8	Positive relationship HR: 4* [37,38,43,52]	HR: 6** [18,19,21,38,52,69]	Conflicting evidence	* Leys et al. [38]: medial OA; Mascarenhas et al. [52]: lateral OA ** Leys et al. [38]: lateral OA; Mascarenhas et al. [52]: medial OA

Abbreviations: ACL, anterior cruciate ligament; BMI, body mass index; BPTB, bone-patellar tendon-bone; HT, hamstring tendon; HR, high-risk of bias studies; LR, low-risk of bias studies; OA, osteoarthritis.

Table 3. Influence of determinants on patellofemoral radiological OA outcome in operatively and operatively/ non-operatively treated cohorts

Group	Determinant	n studies	Significant relationship LR / HR: n studies	No significant relationship LR / HR: n studies	Best Evidence Synthesis	Comments
Patient characteristics	Older age	3	Positive relationship: HR: 2 [37,42]	LR: 1 [56]	Conflicting evidence	
	Higher BMI	2		LR: 1 [56] HR: 1 [42]	Limited evidence for no relationship	
Intra-articular	Meniscal injury/ meniscectomy	3	Positive relationship: HR: 1 [41]	LR: 1 [56] HR: 1 [37]	Conflicting evidence	
	Longer time between injury and reconstruction	3		LR: 1 [56] HR: 2 [37,42]	Moderate evidence for no relationship	
	ACL reconstruction versus non-operative treatment	5	Positive relationship: HR: 2 [31,41]	HR: 3 [19,47,70]	Conflicting evidence	
	Graft type BPTB versus HT	6	Positive relationship: HR: 1 [19]	HR: 5 [18,37,38,52,69]	Limited evidence for no relationship	
	Tunnel placement	2		LR: 1 [56] HR: 1 [62]	Limited evidence for no relationship	

Abbreviations: ACL, anterior cruciate ligament; BMI, body mass index; BPTB, bone-patellar tendon-bone; HT, hamstring tendon; HR, high-risk of bias studies; LR, low-risk of bias studies; OA, osteoarthritis.

Table 4. Influence of determinants on radiological OA outcome compartment unspecified in operatively and operatively/ non-operatively treated cohorts

Group	Determinant	n studies	Significant relationship LR / HR: n studies	No significant relationship LR / HR: n studies	Best Evidence Synthesis	Comments
Patient characteristics	Older age	9	Positive relationship: HR: 3 [50,65,78]	LR: 1 [35] HR: 5 [25,67,68,75,79]	Conflicting evidence	
	Higher BMI	5	Positive relationship: HR: 2 [65,68]	LR: 1 [35] HR: 2 [67,79]	Conflicting evidence	
	Male sex	6	Positive relationship: HR: 1 [68]	LR: 1 [35] HR: 4 [25,67,75,79]	Moderate evidence for no relationship	
Physical examination	Laxity	3		LR: 1 [35] HR: 2 [34,45]	Moderate evidence for no relationship	
	Range of motion loss	4	Positive relationship: HR: 1 [50]	LR: 1 [35] HR: 2 [34,45]	Moderate evidence for no relationship	
	Performance single-legged hop test	3	Negative relationship: HR: 1 [45]	LR: 1 [35] HR: 1 [34]	Conflicting evidence	
Activity	Activity level before reconstruction	2		LR: 1[35] HR: 1 [68]	Limited evidence for no relationship	
Intra-articular	Chondral injury	8	*Medial chondral injury:* Positive relationship: HR: 1 [68] *Lateral chondral injury:* None *Patellar chondral injury:* Positive relationship: HR: 1 [68] *Location not reported* Positive relationship: LR: 1 [35] HR: 3 [33,50,73]	*Medial chondral injury:* none *Lateral chondral injury:* HR: 1 [68] *Patellar chondral injury:* none *Location not reported* HR: 3 [23,25,49]	*Medial chondral injury:* Limited evidence for positive relationship *Lateral chondral injury:* Limited evidence for no relationship *Patellar chondral injury:* Limited evidence for positive relationship *Location not reported* Conflicting evidence	.

Table 4. Influence of determinants on radiological OA outcome compartment unspecified in operatively and operatively/ non-operatively treated cohorts (continued)

Group	Determinant	n studies	Significant relationship LR / HR: n studies	No significant relationship LR / HR: n studies	Best Evidence Synthesis	Comments
	Meniscal injury/ meniscectomy	19	Positive relationship: Medial meniscal injury/ meniscectomy: LR: 1 [35] HR: 5 [49, 55, 67, 68: concurrent*, 75]	Medial meniscal injury/ meniscectomy: HR: 1 [68: prior*]	Medial meniscal injury/ meniscectomy: Moderate evidence positive relationship	* Li et al. [68]; concurrent: meniscectomy concurrent with ACL reconstruction; prior: meniscectomy prior to ACL reconstruction
			Lateral meniscal injury/ meniscectomy: none	Lateral meniscal injury/ meniscectomy: LR: 1 [35] HR: 4 [49, 67, 68: prior and concurrent, 75]	Lateral meniscal injury/ meniscectomy: Moderate evidence no relationship	
			Both meniscectomy: 1 [49]	Both meniscectomy None	Both meniscectomy: Limited evidence for positive relationship	
			Location not reported: HR: 9 [36,39,50,51,54,70,73,74,78]	Location not reported: HR: 4 [23,32,59,79]	Location not reported: Conflicting evidence	
	Longer time between injury and reconstruction	7	Positive relationship HR: 4 [36,68,74,78]	LR: 1 [35] HR: 2 [25,79]	Conflicting evidence	
	ACL reconstruction (versus non-operative treatment)	5	Positive relationship: HR: 1 [65]	HR: 2 [30,79]	Conflicting evidence	
			Negative relationship: HR: 2 [72,77]			
	Graft type BPTB (versus HT)	7	Positive relationship: HR: 5 [24,29,38,45,68]	HR: 2 [23,28]	Conflicting evidence	
	Graft type allograft (versus autograft)	2	Positive relationship: HR: 1 [68]	HR: 1 [26]	Conflicting evidence	
	Tunnel placement	4	Positive relationship: HR: 1 [68]	HR: 3 [38,46,58]	Limited evidence for no relationship	
	Single bundle (versus double bundle)	2		HR: 2 [25,27]	Limited evidence for no relationship	

Abbreviations: ACL, anterior cruciate ligament; BMI, body mass index; BPTB, bone-patellar tendon-bone; HT, hamstring tendon; HR, high-risk of bias studies; LR, low-risk of bias studies; OA, osteoarthritis.

development of knee OA and lateral chondral injury showed no relationship. Ten other studies[23,25,33,35,37,49,50,60,66,73], of which one low-risk of bias study[35], showed conflicting evidence if the location of the chondral injury was not reported.

In 9 studies[20,35,49,55-57,67,68,75], of which 2 were low-risk of bias studies, a distinction between medial and lateral *meniscal injury/ meniscectomy* was made. We found moderate evidence for a positive relationship between medial meniscal injury/ meniscectomy and development of OA (tibiofemoral and unspecified) in patients with an ACL rupture. Conflicting evidence was found for influence of lateral meniscal injury/ meniscectomy on tibiofemoral OA development and moderate evidence for no significant relationship on OA development in compartment unspecified. Twenty-one high-risk of bias studies did not report the location of the meniscal injury; these studies showed limited evidence for positive relationship with development of tibiofemoral OA and conflicting evidence if the compartment of OA development was unspecified. The studies did not report the extent of meniscectomy. Results of meniscal injury/ meniscectomy showed conflicting evidence for a relationship with patellofemoral OA development. One low-risk of bias[56] and one high-risk[37] of bias study reported no significant relationship and in one high-risk of bias study[41] meniscal injury/ meniscectomy was related with patellofemoral OA development.

In seven studies[37,42,43,56,60,61,66], one of them low-risk of bias, moderate evidence for no relationship was found for the influence of *time between injury and reconstruction* on development of tibiofemoral and patellofemoral OA. Seven studies did not specify the compartment of OA outcome and these studies showed conflicting evidence.[25,35,36,68,74,78,79]

In thirteen studies investigating *ACL reconstruction versus non-operative treatment*, conflicting evidence was found with patellofemoral OA[19,31,41,47,70], tibiofemoral OA [19,31,40,53,70,80] and if no specific compartment[30,65,72,77,79] was reported.

Fourteen studies reported outcomes on the relationship between *bone-patellar tendon-bone graft versus hamstring tendon graft* and development of tibiofemoral OA or OA in compartment unspecified. The studies gave conflicting findings. Mascarenhas et al.[52] and Leys et al.[38] reported opposite results for the development of medial and lateral tibiofemoral OA; Mascarenhas et al. found a positive relationship between bone-patellar tendon-bone graft and development of lateral tibiofemoral OA, whereas Leys et al. found a positive relationship between bone-patellar tendon-bone graft and development of medial tibiofemoral OA. In 6 studies[18,19,37,38,52,69], the influence of graft type on patellofemoral OA was studied: limited evidence was found for no relationship.

Conflicting evidence in 2 high-risk of bias studies[26,68] was found for the influence of *allograft* on OA development in compartment unspecified.

One low-risk of bias and 5 high-risk of bias studies reported on the influence of *tunnel placement* of the ACL reconstruction and OA development. Two studies showed no significant relationship between tunnel placement and patellofemoral OA development.[56,62] Four high-risk of bias studies[38,46,58,68] evaluated the influence on development of OA in compartment unspecified; three studies [38,46,58] found no significant relationship, resulting in limited evidence for no relationship.

Two studies with high-risk of bias reported on the influence of double- and single bundle ACL reconstruction and OA development in compartment unspecified.[25,27] These studies showed limited evidence for no relationship with development of OA.

DISCUSSION

We summarised the available evidence concerning which determinants influence the risk of OA after ACL rupture. Sixty-four studies were included, but sixty-two were classified as high-risk of bias.

Key clinically relevant findings

There was moderate evidence for:

- Medial meniscal injury/ meniscectomy influencing OA development (tibiofemoral OA and compartment unspecified).
- No relationship with time between injury and reconstruction and OA development in both patellofemoral and tibiofemoral compartment.
- No relationship between OA development in unspecified compartments and the following determinants was found: sex, laxity, range of motion and lateral meniscal injury/ meniscectomy.

There was limited evidence for influencing OA development:

- Medial and patellar chondral injury (compartment unspecified).
- Meniscal injury/ meniscectomy if the location was not reported (tibiofemoral OA).
- Meniscectomy of both menisci (compartment unspecified).
- Meniscectomy in non-operatively treated patients.

The following determinants showed limited evidence for no relationship with OA development:

- Body mass index (patellofemoral OA).
- Graft type (patellofemoral OA).
- Activity level before -reconstruction (compartment unspecified).
- Lateral chondral injury (compartment unspecified).
- Tunnel placement (patellofemoral OA and compartment unspecified).
- Single versus double bundle ACL-reconstruction technique (compartment unspecified).

Outcome measure – osteoarthritis

Notably, most studies reported only radiological OA. Only 2 studies[43,70] reported both radiological OA and clinical OA as outcomes for evaluating the influence of determinants. Thus, the findings of this systematic review address the influence on radiological OA and not on clinical OA. We were also interested in determinants that influence early degenerative changes, however, the majority of the included studies reported mid- or long-term follow-up. A mean follow-up time ≤ 5 years was reported in only 8 studies.

The role of the meniscus – keep or cut?

Many studies evaluated the influence of the meniscus on the development of OA. The majority of studies did not report the location of the tear, the extent of meniscectomy, and in which compartment OA was developing. We had no information about the influence of the time of the meniscal injury, also a possible confounder.

Although more extended, our results are in line with the findings of the previous reviews concerning meniscal injury and meniscectomy as risk factors for tibiofemoral OA development. However, these previous reviews did not distinguish between medial and lateral meniscal injuries/ meniscectomies.

Our review provides important data that medial meniscal injury/ meniscectomy showed a relationship with the development of OA, but lateral meniscal injury/ meniscectomy did not. Anatomically, the medial meniscus is more rigid with less anterior posterior mobility than the more mobile lateral meniscus, this could have an effect on the secondary OA changes of the affected compartment.[82]

These findings contradict the results of a systematic review concerning clinical outcome and risk of OA development in patients undergoing meniscectomy. In that review, Salata et al.[83] found 4 studies with a higher rate of OA in the lateral meniscectomy group, 2 studies reporting no significant difference, and one study in which medial meniscectomy was more related with OA. These results were not included in our systematic review because the meniscal studies did not meet the inclusion criteria. Moreover, most studies did not report the location (medial or lateral compartment) of the meniscal resection making it difficult to discern the specific influence of medial/ lateral meniscectomy.

A possible explanation for conflicting evidence for development of OA (compartment unspecified) and limited evidence for positive relationship with development of tibiofemoral OA is the heterogeneity of the location of meniscectomy. Also, the included studies did not report the extent of meniscectomy, except the study of Fink et al.,[30] which found in patients treated non-operatively for their ACL rupture a significant correlation between the degree of OA and the amount of meniscal resection that was performed at the time of the initial arthroscopy. For the ACL reconstructed group there was no significant correlation.

A focus on patellofemoral OA

Patellofemoral OA is gaining consideration as an important clinical entity.[84] Regarding OA of the patellofemoral joint, two studies[37,56] found no relationship with meniscal injury/ meniscectomy in an ACL reconstructed population. However, in the study of Keays et al.[37] the relationship was close to significant and in another study meniscal injury/ meniscectomy was significantly associated with patellofemoral OA.[41] Furthermore, in a population without ACL injury meniscectomy was related to development of patellofemoral OA.[85] An explanation for this relationship could be the influence of altered biomechanics in the knee or the meniscal tear was a feature of the already existing early knee OA.

The results of this systematic review confirm the thoughts about the importance of preservation of the meniscus for preventing development of OA. Our advice for future studies is to document the location and extent of meniscectomy as well as which knee compartments, medial, lateral or patellofemoral were used for assessing OA development.

Three key clinical questions and our findings

In clinical practice, three questions are important with regard to choice of treatment for ACL injuries and the development of knee OA.

1) What is the influence of operative versus non-operative treatment on OA development?

Based on our results, we cannot answer this question because there was conflicting evidence. However, we should note that, in the operatively treated patients, the graft type was mostly bone-patellar tendon-bone.[30,31,40,41,47,53,65,70,72,77,79,80] So, there is less information on hamstring tendon reconstructed patients versus non-operatively treated patients and development of OA, despite both grafts types being commonly used for ACL reconstruction.[86]

2. When operative treatment is chosen, what is the influence of graft choice?
Based on the results of this systematic review we cannot recommend one graft type to reduce OA risk.

3. Is early reconstruction necessary for preventing OA development?
The aim of early timing of reconstruction after ACL rupture is to prevent new meniscal and cartilage damage. Our results indicate that early or late reconstruction is not related to greater risk of patellofemoral or tibiofemoral OA.

However, for the OA development in unspecified compartment OA, we cannot give any indication which time point, early or late after injury, is best for reconstruction with regard to preventing OA development. A possible explanation for these conflicting results is the heterogeneity of additional injuries in the included studies and differences in the definition of early reconstruction. Furthermore, Smith et al.[87] found in their meta-analysis no significant difference in the incidence of chondral and meniscal injuries between early and delayed reconstruction groups (the latter was defined as a minimum of 6 weeks post-injury). Another explanation might be that degenerative changes develop after the initial trauma caused by for example traumatic bone marrow lesions and activation of pro-inflammatory cytokines, independently of the choice of treatment. [3] Besides, ACL reconstruction is a new trauma with additional damage such as bone marrow lesions, haemarthrosis and inflammation-related factors, e.g. inflammatory cytokines.

Other considerations
We did not distinguish between partial and complete ACL tears. Partial or complete tears need to be diagnosed by arthroscopic evaluation, the reference for diagnosing ACL rupture. We may assume that the studies that included operatively treated patients, enrolled patients with complete ACL tears. However, most studies did not describe their arthroscopic findings. Of the 4 studies which included non-operatively treated patients, one study[64] reported inclusion of both partial and complete tears, two studies[22,76] reported inclusion of only complete tears and one study[71] did not describe the type of the ACL tear. Thus, it is difficult to draw conclusions about the difference between the influence of partial and complete tears on OA development. Besides, in long-term follow-up studies it is possible that partial tears progress to complete ACL tears[88] and then it is difficult to distinguish the contribution of the partial and complete tear to the development of OA.

A determinant, which was not included in the results, is altered knee biomechanics after ACL injury. Possible explanation for no information about this determinant is that studies researching altered knee biomechanics include fewer patients (n = <

20, exclusion criteria of this systematic review) and that these studies have a cross-sectional design (exclusion criteria of this systematic review). Chaudari et al.[89] suggest that the observed changes in the knee biomechanics result in altered loading patterns and influence metabolic changes in the underlying cartilage. Reduced internal tibial rotation was found in patients after ACL reconstruction compared to the contralateral knee and healthy controls.[90] In addition to this finding, a recently published cross-sectional study showed that after ACL reconstruction, patients with patellofemoral OA and valgus alignment had significantly less internal knee rotation during walking and running than patients with valgus alignment and no patellofemoral OA.[91] However this study had a cross-sectional design; prospective studies are required to evaluate if the altered knee rotation is a result of patellofemoral OA or influences the development of patellofemoral OA.

Limitations

This systematic review has some limitations. First, of the 64 included studies, only 14[23,26,34,35,38,42,43,46,47,56,65,67,68,70] corrected for the influence of confounders. Consequently, the reported influence of determinants on the development of OA may be partly or completely explained by other factors. By presenting the data, one of the criteria to be classified as low-risk of bias study, was controlling for confounding. Prospective observational study design is the best way to determine predictors for development of OA after an ACL rupture. However, prospective collected data and retrospective analyses (research question defined after data collection) was also useful for our research question. Therefore, we also included retrospective study designs.

Second, the number of patients available for analysis at follow-up in the included studies was small. Only 18 of the 64 (28%) included studies had more than 100 patients available for analysis at follow-up.

Third, the included studies were heterogeneous with regard to study design, determinant assessment, additional intra-articular injuries, reported OA outcome, definition of OA, and the statistical methods used. For these reasons, comparison between the included studies was difficult and pooling of the data was not possible. Therefore, we used the second best option for presenting the results: best-evidence synthesis.

Best-evidence synthesis is appropriate for summarising the available evidence. All 64 included studies were classified as low- or high-risk of bias; however, only 2 studies met the criteria for low-risk of bias. This means that reporting of inclusion of consecutive patients, measuring of determinant and outcome independently, using accurate measures for the determinants and description of loss to follow-up with maximal 20% and correction for confounding were poorly performed and described in the included studies.

Finally, we attempted to evaluate the influence of determinants on the development of tibiofemoral and patellofemoral OA separately. However, we should note that some studies did not use a valid tool for the compartmental assessment of OA, (e.g. Kellgren and Lawrence score for assessment of patellofemoral OA). In some studies the compartment was not described (compartment unspecified). The evaluation of the correctly used classification system for compartmental OA assessment was not included in the quality assessment tool.

Strengths

The strengths of this systematic review are that we summarised the evidence for tibiofemoral OA and patellofemoral OA outcomes after ACL injury separately. Moreover, we summarised these outcomes in patients who had had ACL reconstruction and those who had been managed with conservative treatment. Additionally, we evaluated determinants that influence early degenerative changes because we included studies with relatively short follow-ups (a minimum of 2 years). To be comprehensive, we chose to include both prospective and retrospective study designs having at least 20 patients. In addition to previously published systematic reviews,[5-7] we included 21 studies published after the search dates of those systematic reviews.

Studies that used out-dated surgery techniques were excluded which resulted in exclusion of many older studies. However, our oldest study included was published in 1989[64] and newer studies might be of better quality as our two low-risk of bias studies were published in 2012[56] and 2013[35]. The best evidence synthesis considers the quality of the studies and accounts for a possible bias. When we analysed the results of studies only published during the last 10 years, the results differed minimally. The only aspects that changed were the influence of chondral injury (location not reported) on OA development (compartment unspecified), and of the graft type bone-patellar tendon-bone; both would change from conflicting evidence to limited evidence for a positive relationship with development of OA. These results of limited evidence still need more high quality studies in order to make firm recommendations.

Overall, we can conclude that despite the inclusion of many new studies in this comprehensive systematic review, including two low-risk of bias studies[35,56], more low-risk of bias studies are required to evaluate determinants and their role in OA development. Many determinants showed conflicting and limited evidence. The following determinants should be further studied in large prospective studies, which could be used for meta-analysis: knee function and activity level, both examined in the first period after ACL rupture, patients characteristics, such as age, body mass index and sex, meniscal injury/ meniscectomy specified in medial and lateral compartments, meniscal repair, chondral injury, choice of treatment, graft type and reconstruction technique. We strongly recommend specifying the compartment of OA development.

In summary, medial meniscal injury/ meniscectomy after ACL rupture influences the development of OA (tibiofemoral OA and compartment unspecified). In contrast, it seems that lateral meniscal injury/ meniscectomy has no relationship with OA development. Our results also suggest that time between injury and reconstruction does not influence the development of patellofemoral and tibiofemoral OA. However, we found limited or conflicting evidence for many determinants.

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Summary Box: what are the new findings?

In patients with an ACL rupture:

1. Moderate evidence was found that medial meniscal injury/ meniscectomy had influence on OA development; in contrast, lateral meniscal injury/ meniscectomy showed moderate evidence for no relationship with development of OA.
2. Time between injury and reconstruction showed moderate evidence for no relationship with patellofemoral and tibiofemoral OA development.
3. It is still unclear which treatment option is the best for preventing OA development; conflicting evidence was found between treatment choice (operative versus non-operative treatment) and development of knee OA.

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APPENDICES

Appendix Table 1. Quality Assessment

Paper ID:
Reviewer:
Study design:

Question		Response	Scoring
1.	A clearly stated aim	Did they have a "study question" or "main aim" or "objective"? The question addressed should be precise and relevant in light of available literature. To be scored *adequate* the aim of the study should be coherent with the "Introduction" of the paper.	☐ 1. adequate ☐ 0. inadequate ☐ 0. not reported
2.	Inclusion of consecutive patients	Did the authors say: "consecutive patients" or "all patients during period from … to…." or "all patients fulfilling the inclusion criteria".	☐ 1. adequate ☐ 0. inadequate ☐ 0. not reported
3.	A description of inclusion and exclusion criteria	Did the authors report the inclusion and exclusion criteria?	☐ 1. adequate ☐ 0. inadequate ☐ 0. not reported
4.	Inclusion of patients	Did the authors report how many eligible patients agreed to participate (i.e. gave consent)?	☐ 1. adequate ☐ 0. inadequate ☐ 0. not reported
5.	Prospective collection of data. Data were collected according to a protocol established before the beginning of the study.	Did they say "prospective" or "follow-up"? The study is NOT PROSPECTIVE when: • chart review, or database review • "retrospective"	☐ 1. adequate ☐ 0. inadequate ☐ 0. not reported
6.	Outcome measures	Did they report the OA outcome; clinical OA, osteotomy, total knee arthroplasty, unilateral knee arthroplasty, radiographic OA, OA findings on MRI, OA findings during arthroscopy?	☐ 1. adequate ☐ 0. inadequate ☐ 0. not reported
7.	Was the used OA classification shown to be valid and reliable?	To be scored as *adequate*, the following classifications or indications could be used: • Clinical: ACR criteria, osteotomy, total knee arthroplasty, unilateral knee arthroplasty • Radiographic OA: Kellgren & Lawrence, Fairbank, Ahlback, IKDC grading system, OARSI grading system. • MRI: use of description of definite osteophyte formation and cartilage loss • Arthroscopic: Outerbridge classification • Combination of above-mentioned classifications/ indications. To be scored as *inadequate*: • Use of self-formulated classifications • Use of modified classifications	☐ 1. adequate ☐ 0. inadequate ☐ 0. not reported

8.	Unbiased assessment of the study outcome and determinants	To be judged as *adequate* the following 2 aspects had to be positive: • Outcome and determinants had to be measured independently • Both for cases and controls the outcome and determinants had to be assessed in the same way	☐ 1. adequate ☐ 0. inadequate ☐ 0. not reported
9.	Were the determinant measures used accurate (valid and reliable)?	For studies where the determinant measures are shown to be valid and reliable, the question should be answered *adequate*. For studies which refer to other work that demonstrates the determinant measures are accurate, the question should be answered as *adequate*. For example: a meniscal rupture had to be scored during arthroscopy or on MRI; activity level had to be measured with a validated questionnaire.	☐ 1. adequate ☐ 0. inadequate ☐ 0. not reported
10.	Follow-up period appropriate to the aim of the study	Did they report the follow-up period? To be judged as *adequate*: • the follow-up should be sufficiently long to allow the assessment of the main outcome: for radiographic OA a minimum of 4 years and for OA findings on MRI or during arthroscopy a minimum of 2 years.	☐ 1. adequate ☐ 0. inadequate ☐ 0. not reported
11.	Loss to follow-up	To be judged as *adequate* the following 2 aspects had to be positive: • Did they report the losses to follow-up? • Was the loss to follow-up less than 20%	☐ 1. adequate ☐ 0. inadequate ☐ 0. not reported
12.	Adequate Statistical analyses	To be judged as *adequate* the following 3 aspects had to be positive: • There must be a description of the relationship between the determinant and OA outcome or a description of the comparison (with information about the statistical significance) • Was there adjustment for the following confounders: a. Age b. Gender c. BMI If the effect of the main confounders was not investigated or confounding was demonstrated but no adjustment was made in the final analyses, the question should be answered *inadequate*. • Did they show variance in the reported outcome (for example SD, CI)	☐ 1. adequate ☐ 0. inadequate ☐ 0. not reported

Abbreviations: ACR, American College of Rheumatology; BMI, body mass index; CI, confidence interval; IKDC, International Knee Documentation Committee; MRI, magnetic resonance imaging; OA, osteoarthritis; SD, standard deviation.

Appendix Table 2. Characteristics of included studies (n=64)

	Study design	Number of patients (used for analysis)	Age at start study, years	Sex,% male	Follow-up time	OA outcome	Knee compartment	Definition OA	RBA
Aglietti 1994[54]	retrospective study	57	not reported	not reported	meniscal repair group: mean 55 (range 36-71) months; meniscectomy group: mean 52 (range 36-90) months; normal meniscal group: mean 57 (range 37-77) months	radiographic: the Hospital for Special Surgery(HSS) radiographic score	tibiofemoral (medial and lateral) and patellofemoral	< 26 points	HR
Aglietti 1997[55]	retrospective study	77	mean 23 (range 15-40)	81	mean 7 (range 5.4-8.6) years	radiographic: JSN (no specific definition)	not reported	not reported	HR
Ahlden 2009[18]	RCT	44	BPTB group: median 26 (range 14-48); hamstring group: median 29 (range 15-40)	68	BPTB group: median 89 (range 77-110) months hamstring group: median 86 (range 69-109) months	radiographic: Ahlbäck and Fairbank score / presence of osteophytes	tibiofemoral (medial and lateral) and patellofemoral	not reported	HR
Ahn 2012[56]	retrospective study	117	mean 29.2 (SD 8.8)	75.2	mean 10.3 (SD 1) years	radiographic: IKDC grading system	tibiofemoral (medial and lateral) and patellofemoral	grade C and D	LR
Cohen 2007[57]	retrospective study	62	mean 27 (range 15-46)	76	mean 11 years 2 months (range 10-15 years)	radiographic; Fairbank score	tibiofemoral (medial and lateral)	not reported	HR

Appendix Table 2. Characteristics of included studies (n=64) continued

	Study design	Number of patients (used for analysis)	Age at start study, years	Sex,% male	Follow-up time	OA outcome	Knee compartment	Definition OA	RBA
Fink 2001[30]	prospective follow-up study	84	ACL reconstruction group: mean 33.6 (SD 8.0); non-operative group: mean 32.3 (SD 9.9)	ACL reconstruction group: 80; non-operative group: 72	ACL reconstruction group: mean 74.2 months; non-operative group: mean 84.2 months	radiographic: modified Fairbank score	tibiofemoral	not reported	HR
Fithian 2005[31]	prospective follow-up study	209	mean 39 (range 16 - 69)*	48	mean 6.6 (range 3 - 10) years	radiographic: IKDC grading system	tibiofemoral (medial and lateral) and patellofemoral	not reported	HR
Frobell 2013[19]	RCT	113	early ACL reconstruction group: mean 26.4 (SD 5.1); delayed optional ACL reconstruction group: mean 25.8 (SD 4.7)	early ACL reconstruction group: 80; delayed optional ACL reconstruction group: 66	early ACL reconstruction group: mean 60 (95% CI 59 to 61) months; delayed ACL reconstruction group: mean 59 (95% CI 57 to 60) months; rehabilitation alone group: mean 58 (95% CI 55 to 61) months	radiographic: grading according to atlas of OARSI	tibiofemoral and patellofremoral	JSN ≥2 in compartment, a sum of osteophyte grades ≥ 2 in the same compartment or grade 1 JSN combined with grade 1 osteophyte in same compartment	HR
Gerhard 2013[58]	retrospective study	63	mean 27 (SD 7)	86	mean 16 (SD 1) years	radiographic: Kellgren and Lawrence score	not reported	not reported	HR

Appendix Table 2. Characteristics of included studies (n=64) continued

	Study design	Number of patients (used for analysis)	Age at start study, years	Sex,% male	Follow-up time	OA outcome	Knee compartment	Definition OA	RBA
Giron 2005[32]	prospective follow-up study	38	mean 29 (range 17-53)	79	5 years†	radiographic: IKDC grading system	not reported	not reported	HR
Hanypsiak 2008[33]	prospective follow-up study	44	39*	70	mean 12.7 (range 11.8-13.8) years	radiographic: Rosenberg	not reported	JSN ≥ 2 mm compared to uninvolved contralateral compartment	HR
Harilainen 2006[20]	RCT	71	not reported	not reported	median 5 years (range 3 years 11months-6 years 7 months)	radiographic: IKDC grading system	tibiofemoral (medial and lateral)	not reported	HR
Hart 2005[59]	retrospective study	31	mean: 27.8 (range 18-47)	68	mean 10 years (range 9-13)	radiographic: Ahlbäck score	tibiofemoral (medial and lateral) and patellofemoral	Ahlbäck grade ≥ 1	HR
Holm 2010[21]	RCT	57	hamstring group: mean 27 (SD 9); BPTB group: 25 (SD 7)	hamstring group 52; BPTB group: 64	hamstring group: mean 10.7 (SD 0.4) years; BPTB group: 10.2 (SD 0.4) years	radiographic: Kellgren and Lawrence score	tibiofemoral	Kellgren & Lawrence score ≥ 2	HR
Hui 2011[34]	prospective follow-up study	59	mean 25 (range 15-42)	51	mean 184 (range 169-199) months	radiographic: IKDC grading system	not reported	not reported	HR

Appendix Table 2. Characteristics of included studies (n=64) continued

	Study design	Number of patients (used for analysis)	Age at start study, years	Sex,% male	Follow-up time	OA outcome	Knee compartment	Definition OA	RBA
Ichiba 2009[60]	retrospective study	46	mean 26 (range 13-39)	26	mean 3.9 (range 2-8) years	radiographic: Kawakubo method	tibiofemoral	Increase OA score: differences between preoperative OA score and at follow-up	HR
Janssen 2013[35]	prospective follow-up study	86	mean 31.2 (SD 8.0)	66	mean 10 (SD 0.7) years	radiographic: Ahlbäck and Kellgren and Lawrence score	not reported	Ahlbäck grade 1 and Kellgren and Lawrence grade 3	LR
Jarvela 1999[61]	retrospective study	91	early reconstruction group: 32 (range 15-61); late reconstruction group: 30 (range 16-46)	69	mean 7 (range early reconstruction group 5.9-8.5; late reconstruction group range 4.6-8.8) years	radiographic: IKDC grading system	medial tibiofemoral	IKDC grade ≥ nearly normal‡	HR
Jarvela 2001[62]	retrospective study	86	mean 31 (range 15-61)	70	mean 7 (range 4.6-8.8) years	radiographic: IKDC grading system	patellofemoral	IKDC evaluation system ≥ mild	HR

Appendix Table 2. Characteristics of included studies (n=64) continued

	Study design	Number of patients (used for analysis)	Age at start study, years	Sex,% male	Follow-up time	OA outcome	Knee compartment	Definition OA	RBA
Jarvela 2001[63]	retrospective study	72	isolated ACL rupture group: mean 29 (SD 9); ACL tear accompanying injuries group: mean 34 (SD 12)	67	isolated ACL rupture group: mean 7.1 (SD 0.7) years; ACL tear accompanying injuries group: mean 6.9 (SD 0.7) years	radiographic: IKDC grading system	tibiofemoral and patellofemoral	not reported	HR
Jomha 1999[36]	prospective follow-up study	53	acute ACL tears group: mean 27; chronic ACL tear group: mean 28	70	7 years†	radiographic: IKDC grading system	not reported	presence of osteophytes, subchondral sclerosis, change of articular surface, or JSN	HR
Kannus 1989[64]	retrospective study	77	mean 30 (SD 11)*	75.3	mean 7.8 (SD 2.0) years	radiographic: classification according to Kannus (0-100 point scale)	tibiofemoral (medial and lateral) and patellofemoral	score 95-99: good; score 90-94: fair; ≤ 89: poor	HR
Keays 2010[37]	prospective follow-up study	56	mean 27 (range 18-38)	71	6 years†	radiographic: modified Kellgren and Lawrence score (grade 0-3)	tibiofemoral and patellofemoral	Modified Kellgren & Lawrence score ≥ 1	HR
Kessler 2008[65]	retrospective study	109	mean 30.7 (range 12.5-54.0)	62.4	mean 11.1 (range 7.5-16.3) years	radiographic: Kellgren and Lawrence score	not reported	Kellgren & Lawrence score > 1	HR

Appendix Table 2. Characteristics of included studies (n=64) continued

	Study design	Number of patients (used for analysis)	Age at start study, years	Sex,% male	Follow-up time	OA outcome	Knee compartment	Definition OA	RBA
Lebel 2008[66]	retrospective study	98	mean 28.8 (SD 8.3)	77	mean 11.6 (SD 0.8) years	radiographic: IKDC grading system	tibiofemoral	not reported	HR
Leiter 2013[67]	retrospective study	68	mean 31.2 (SD 9.1)	63	mean 14.6 (SD 1.9) years	radiographic: Kellgren and Lawrence score	not reported	not reported	HR
Leys 2012[38]	prospective follow-up study	109	BPTB group: median 25 (range 15-42); hamstring group: median 24 (range 13-52)	53	15 years†	radiographic: IKDC grading system	tibiofemoral (medial and lateral) and patellofemoral	not reported	HR
Li 2011[68]	retrospective study	249	mean 26.4 (SD 10.2)	61.4	mean 7.9 (range 2.1-20.3) years	radiographic: Kellgren and Lawrence score	not reported	2 grade difference between index and contralateral in at least 2 compartments or 1 grade difference between knees in at least 2 compartments	HR
Liden 2008[69]	retrospective study	113	median 28 (range 15-59)	69	median 86 (range 67-111) months	radiographic: Ahlbäck and Fairbank score / unknown system	tibiofemoral and patellofemoral	not reported	HR

Appendix Table 2. Characteristics of included studies (n=64) continued

	Study design	Number of patients (used for analysis)	Age at start study, years	Sex,% male	Follow-up time	OA outcome	Knee compartment	Definition OA	RBA
Lohmander 2004[70]	retrospective study	67	mean 19 (range 14-28)	0	12 years†	radiographic: grading according to atlas of OARSI	tibiofemoral and patellofemoral	JSN grade of ≥ 2 or a sum of ≥ 2 for the 2 marginal osteophyte grades from the same compartment, or a JSN grade of at least 1 in combination with an osteophyte grade of at least 1 in the same compartment	HR
Mascarenhas 2012[52]	matched case control study	46	mean 18 (SD 3)	43	BPTB group: mean 5 (SD 2) years; hamstring group: mean 4 (SD 2) years	radiographic: Kellgren and Lawrence score	tibiofemoral (medial and lateral) and patellofemoral	not reported	HR
Menke 1990[71]	retrospective study	90	not reported	94	5 to 12 years	radiographic: Tapper and Hoover grading system	not reported	not reported	HR
Meuffels 2009[53]	matched case control study	50	operative group: mean 37.6 (SD 6.2); non-operative group: mean 37.8 (SD 6.8)*	76	10 years†	radiographic: Kellgren and Lawrence score	tibiofemoral	Kellgren & Lawrence score ≥ 2	HR

Appendix Table 2. Characteristics of included studies (n=64) continued

	Study design	Number of patients (used for analysis)	Age at start study, years	Sex,% male	Follow-up time	OA outcome	Knee compartment	Definition OA	RBA
Meunier 2007[22]	RCT	36	non-operative group: mean 21 (range 14-30)	62.5	mean 15 (SD 1) years	radiographic: Ahlbäck and Fairbank score	not reported	Ahlbäck and Fairbank grade > 0	HR
Mihelic 2011[72]	retrospective study	54	reconstruction group: mean 25.3; non-operative group: mean 25.5	81	range 17-20 years	radiographic: IKDC grading system	not reported	not reported	HR
Moisala 2007[39]	prospective follow-up study	66	mean 34 (range 16-64)	64	mean 57 months (range 3-8 years)	radiographic: IKDC grading system	not reported	IKDC grading system > A	HR
Murray 2012[73]	retrospective study	83	mean 30 (SD 10)	not reported	mean 13 years	radiographic: IKDC grading system	not reported	IKDC grade C and D	HR
Neuman 2008[40]	prospective follow-up study	79	mean 26 (SD 8)	58	mean 15.7 (SD 1.4) years	radiographic: grading according to atlas of OARSI	tibiofemoral	JSN ≥ grade 2, sum of the 2 marginal osteophyte scores from the same compartment ≥2, or grade 1 JSN in combination with grade 1 osteophyte in the same compartment.	HR

Appendix Table 2. Characteristics of included studies (n=64) continued

	Study design	Number of patients (used for analysis)	Age at start study, years	Sex,% male	Follow-up time	OA outcome	Knee compartment	Definition OA	RBA
Neuman 2009[41]	prospective follow-up study	75	mean 26 (SD 8)	58	mean 15.7 (SD 1.4) years	radiographic: grading according to atlas of OARSI	patellofemoral	JSN of grade 2 or higher in either the medial or lateral compartment, sum of marginal osteophyte grades ≥ 2, or grade 1 JSN in combination with a grade 1 marginal osteophyte.	HR
Oiestad 2013[42]	prospective follow-up study	181	mean 39.1 (SD 8.7)*	58	mean 12.3 (SD 1.2) years	radiographic: Kellgren and Lawrence score	patellofemoral	Kellgren and Lawrence grade ≥ 2	HR
Oiestad 2010[43]	prospective follow-up study	164	mean 27.4 (SD 8.5)	57	mean 12.1 (SD 1.4) years	radiographic: Kellgren and Lawrence score	tibiofemoral	Kellgren & Lawrence score ≥ 2	HR
Oiestad 2010[44]	prospective follow-up study	181	mean 39.5 (8.6) *	57	mean 12.4 (SD 1.2) years	radiographic: Kellgren and Lawrence score	tibiofemoral	Kellgren & Lawrence score ≥ 2	HR

Appendix Table 2. Characteristics of included studies (n=64) continued

	Study design	Number of patients (used for analysis)	Age at start study, years	Sex,% male	Follow-up time	OA outcome	Knee compartment	Definition OA	RBA
O'Neill 2001[23]	RCT	225	not reported	not reported	mean 102 months (range 6-11 years)	radiographic: IKDC grading system	not reported	not reported	HR
Otto 1998[74]	retrospective study	62	mean 27 (range15-46)	72	minimum 5 years	radiographic: IKDC grading system	not reported	not reported	HR
Pinczewski 2007[45]	prospective follow-up study	128	BPTB group median 25 (range 15-42); hamstring group: median 24 (range 13-52)	not reported	10 years†	radiographic: IKDC grading system	not reported	not reported	HR
Pinczewski 2008[46]	prospective follow-up study	184	not reported	not reported	7 years†	radiographic: IKDC grading system	not reported	not reported	HR
Potter 2012[47]	prospective follow-up study	40	mean 37.2 (SD 9.1)	40	maximum 11 years	MRI: modified Outerbridge assessment	tibiofemoral (medial and lateral) and patellofemoral	not reported	HR
Ruiz 2002[48]	prospective follow-up study	30	not reported	93	mean 7 years (range 64-114 months)	radiographic: JSN	tibiofemoral	not reported	HR
Sajovic 2011[24]	RCT	52	hamstring group: mean 36 (range 25-54); BPTB group: mean 38 (range 27-58)*	58	11 years†	radiographic: IKDC grading system	not reported	worst grading compartment was used as overall grade	HR

Appendix Table 2. Characteristics of included studies (n=64) continued

	Study design	Number of patients (used for analysis)	Age at start study, years	Sex,% male	Follow-up time	OA outcome	Knee compartment	Definition OA	RBA
Salmon 2006[75]	retrospective study	43	median 27(95% CI 25-28)	70	minimum 13 years	radiographic: IKDC grading system	not reported	not reported	HR
Segawa 2001[76]	retrospective study	70	mean 22.8 (range 12-50)	40	mean 11.6 (range 5-27) years	radiographic: Kellgren and Lawrence score	not reported	Kellgren & Lawrence score ≥ 1	HR
Seitz 1994[77]	retrospective study	87	operative group: mean 27 (range 15-42); non-operative group: mean 28 (range 18-56)	51	mean 8.5 (range 5-12) years	radiographic: Jäger and Wirth grading system	not reported	not reported	HR
Seon 2006[78]	retrospective study	58	mean 30.4 (range 18-58)*	95	mean 11.2 (range 8.6-13.8) years	radiographic: Kellgren and Lawrence score	not reported	Kellgren and Lawrence > 2	HR
Shelbourne 2000[49]	prospective follow-up study	range 45-282	women: mean 21 (range 13.2-50.1); men: mean 23.7 (range 11.8-53)	73	mean 7.6 (SD 2.3) years	radiographic: IKDC grading system	not reported	IKDC grade ≥ nearly normal‡	HR
Shelbourne 2012[50]	prospective follow-up study	780	mean 25.4 (SD 9.2)	not reported	mean 10.5 (SD 4.5) years	radiographic: IKDC grading system	tibiofemoral (medial and lateral) and patellofemoral	IKDC evaluation system > grade A	HR

Appendix Table 2. Characteristics of included studies (n=64) continued

	Study design	Number of patients (used for analysis)	Age at start study, years	Sex,% male	Follow-up time	OA outcome	Knee compartment	Definition OA	RBA
Song 2013[25]	RCT	112	DB group: mean 30.3 (range 17-50); SB group: mean 35.5 (range 19-58)	DB group: 85; SB group: 63	DB group: mean 5.3 (range 4.1-6.1) years; SB group: mean 5.7 (range 4.1-6.2) years	radiographic: Kellgren and Lawrence score	not reported	≥ 1 grade progression compared with pre-operative condition	HR
Streich 2011[79]	retrospective study	80	mean 25.8 (range 17-39)	70	operative group: mean 15.4 (SD 0.8) years; non-operative group: mean 15.2 (SD 0.7) years	radiographic: IKDC grading system	not reported	IKDC evaluation system > grade A	HR
Sun 2009[26]	RCT	156	autograft group: mean 31.7 (SD 6.3); allograft group: mean 32.8 (SD 7.1)*	79	mean 5.6 (autograft group: SD 1.2; allograft group: SD 1.3) years	radiographic: Kellgren and Lawrence score	not reported	not reported	HR

Appendix Table 2. Characteristics of included studies (n=64) continued

	Study design	Number of patients (used for analysis)	Age at start study, years	Sex,% male	Follow-up time	OA outcome	Knee compartment	Definition OA	RBA
Suomalainen 2012[27]	RCT	65	Double-bundle with bioabsorbable screw group: mean 34 (SD 10); single-bundle with bioabsorbable screw group: mean 30 (SD 8); single-bundle with metallic screw group: mean 33 (SD 10)	Double-bundle with bioabsorbable screw group: 30; single-bundle with bioabsorbable screw group: 30; single-bundle with metallic screw group: 37	5 years†	radiographic: Kellgren and Lawrence score	tibiofemoral and patellofemoral	not reported	HR
von Porat 2004[80]	retrospective study	122	mean 38 (SD 5.2)	100	14 years†	radiographic: Kellgren and Lawrence score	tibiofemoral	Kellgren & Lawrence score ≥ 2	HR
Wang 2004[81]	retrospective study	44	mean 31 (range 19-57)	73	mean 70 (range 46-86) months	radiographic: Ahlbäck rating system	tibiofemoral	not reported	HR
Wipfler 2011[28]	RCT	54	BPTB: mean 29.87 (range 25 to 55); HT: 34.23 (range 26 to 64)	BPTB: 62; HT: 60	mean 8.8 (SD 0.55) years	MRI: International Cartilage Repair Society evaluation	not reported	not reported	HR

Appendix Table 2. Characteristics of included studies (n=64) continued

	Study design	Number of patients (used for analysis)	Age at start study, years	Sex,% male	Follow-up time	OA outcome	Knee compartment	Definition OA	RBA
Wu 2002[51]	prospective follow-up study	34	mean 24 (15-45)	57	mean 10.4 (range 9-13) years	radiographic: Fairbank system	not reported	not reported	HR
Zaffagnini 2011[29]	RCT	79	BPTB group: mean 26 (SD 9.5); hamstring group: mean 27 (SD 9)	53	mean 8.6 (range 8-10) years	radiographic: IKDC grading system	not reported	not reported	HR

*Age at follow-up

†Median or mean of follow-up time not reported

‡For calculation of the relationship between determinant and OA development, we chose a cut-off point.

Abbreviations: BPTB, bone-patellar tendon-bone; CI, confidence interval; HR, high-risk of bias; IKDC, International Knee Documentation Committee; JSN, joint space narrowing; LR, low-risk of bias; OARSI, Osteoarthritis Research Society International; RBA, risk of bias assessment; RCT, Randomized Controlled Trial; SD, standard deviation; WORMS, Whole Organ Magnetic Resonance Imaging Score.

Appendix Table 3. Quality Assessment Score

		Quality Assessment questions												
	RBA*	**2**	**8**	**9**	**11**	**12[a]**	**1**	**3**	**4**	**5**	**6**	**7**	**10**	**12[a,b,c]**
Aglietti 1994 [54]	HR	0	0	1	1	0	1	1	0	0	1	0	0	0
Aglietti 1997 [55]	HR	0	0	1	0	0	1	1	0	0	1	0	1	0
Ahlden 2009 [18]	HR	0	0	1	0	0	1	1	0	1	1	1	1	0
Ahn 2012 [56]	**LR**	**1**	**1**	**1**	**1**	**1**	1	1	0	0	1	1	1	0
Cohen 2007 [57]	HR	1	1	1	0	0	1	1	0	0	1	1	1	0
Fink 2001 [30]	HR	1	0	1	0	0	1	1	1	1	1	1	1	0
Fithian 2005 [31]	HR	0	0	1	0	0	1	1	0	1	1	1	0	0
Frobell 2013 [19]	HR	1	0	1	1	0	1	1	1	1	1	1	1	0
Gerhard 2013 [58]	HR	1	0	1	1	0	1	0	1	0	1	1	1	0
Giron 2005 [32]	HR	0	0	1	1	0	1	1	0	1	1	1	1	0
Hanypsiak 2008 [33]	HR	1	1	1	1	0	1	1	0	1	1	0	1	0
Harilainen 2006 [20]	HR	0	1	1	0	0	1	1	0	1	1	1	0	0
Hart 2005 [59]	HR	1	1	1	0	0	1	1	1	1	1	1	1	0
Holm 2010 [21]	HR	0	0	1	0	0	1	0	1	1	1	1	1	0
Hui 2011 [34]	HR	1	0	1	0	1	1	1	0	1	1	1	1	0
Ichiba 2009 [60]	HR	0	0	1	0	0	1	1	0	0	1	0	0	0
Janssen 2013 [35]	**LR**	**1**	**1**	**1**	**1**	**1**	1	1	1	1	1	1	1	1
Jarvela 1999 [61]	HR	0	0	1	0	0	1	0	0	0	1	0	1	0
Jarvela 2001 [62]	HR	1	0	0	0	0	1	0	1	0	1	1	1	0
Jarvela 2001 [63]	HR	1	0	1	0	0	1	0	0	0	1	1	1	0
Jomha 1999 [36]	HR	1	1	1	0	0	1	1	0	1	1	1	1	0

Appendix Table 3. Quality Assessment Score (continued)

		Quality Assessment questions												
	RBA*	**2**	**8**	**9**	**11**	**12[a]**	**1**	**3**	**4**	**5**	**6**	**7**	**10**	**12[a,b,c]**
Kannus 1989 [64]	HR	0	0	1	0	0	1	1	0	0	1	0	1	0
Keays 2010 [37]	HR	1	1	1	1	0	1	1	1	1	1	0	1	0
Kessler 2008 [65]	HR	0	0	1	1	1	1	1	0	0	1	1	1	0
Lebel 2008 [66]	HR	1	0	1	0	0	1	1	0	1	1	1	1	0
Leiter 2013 [67]	HR	1	1	1	0	1	1	1	0	0	1	1	1	1
Leys 2012 [38]	HR	1	0	1	0	1	1	1	0	1	1	1	1	0
Li 2011 [68]	HR	0	0	1	0	1	1	1	0	0	1	1	1	1
Liden 2008 [69]	HR	1	0	1	1	0	1	1	1	0	1	1	1	0
Lohmander 2004 [70]	HR	1	0	1	0	1	1	1	1	0	1	1	1	1
Mascarenhas 2012 [52]	HR	0	0	1	0	0	1	1	0	0	1	1	0	0
Menke 1990 [71]	HR	0	0	1	0	0	0	0	0	0	1	0	1	0
Meuffels 2009 [53]	HR	0	1	1	0	0	1	1	0	0	1	1	1	0
Meunier 2007 [22]	HR	0	1	1	1	0	1	0	0	1	1	1	1	0
Mihelic 2011 [72]	HR	0	1	1	0	0	1	1	0	0	1	1	1	0
Moisala 2007 [39]	HR	1	0	1	0	0	1	1	0	0	1	1	0	0
Murray 2012 [73]	HR	0	1	1	0	0	1	1	0	0	1	1	1	0
Neuman 2008 [40]	HR	1	0	1	1	0	1	1	1	1	1	1	1	0
Neuman 2009 [41]	HR	1	1	1	0	0	1	0	0	1	1	1	1	0
Oiestad 2013 [42]	HR	0	0	1	1	1	1	1	0	1	1	1	1	1
Oiestad 2010 [43]	HR	1	0	1	1	1	1	1	1	1	1	1	1	1
Oiestad 2010 [44]	HR	1	0	1	1	0	1	1	1	1	1	1	1	0
O'Neill 2001 [23]	HR	0	0	1	0	1	0	0	0	0	1	1	1	0

Appendix Table 3. Quality Assessment Score (continued)

		Quality Assessment questions												
	RBA*	**2**	**8**	**9**	**11**	**12[a]**	**1**	**3**	**4**	**5**	**6**	**7**	**10**	**12[a,b,c]**
Otto 1998 [74]	HR	1	0	1	1	0	1	0	0	0	1	1	1	0
Pinczewski 2007 [45]	HR	1	0	1	0	0	1	1	0	1	1	1	1	0
Pinczewski 2008 [46]	HR	1	1	0	1	1	1	1	0	1	1	1	1	0
Potter 2012 [47]	HR	0	1	1	1	1	1	1	0	1	1	0	1	0
Ruiz 2002 [48]	HR	0	0	1	0	0	1	0	0	1	1	0	1	0
Sajovic 2011 [24]	HR	0	0	1	1	0	1	1	1	1	1	1	1	0
Salmon 2006 [75]	HR	1	1	1	0	0	1	1	0	0	1	1	1	0
Segawa 2001 [76]	HR	0	0	1	0	0	1	1	1	0	1	1	1	0
Seitz 1994 [77]	HR	0	0	1	0	0	1	0	0	0	1	0	1	0
Seon 2006 [78]	HR	1	0	1	1	0	1	0	0	0	1	1	1	0
Shelbourne 2000 [49]	HR	0	0	1	0	0	1	1	0	0	1	1	1	0
Shelbourne 2012 [50]	HR	0	0	1	0	0	1	1	0	1	1	1	1	0
Song 2013 [25]	HR	0	0	1	1	0	1	1	0	1	1	1	1	0
Streich 2011 [79]	HR	1	0	1	1	0	1	1	1	0	1	1	1	0
Sun 2009 [26]	HR	0	0	1	1	1	1	1	1	1	1	1	1	0
Suomalainen 2012 [27]	HR	0	0	1	0	0	1	1	0	1	1	1	1	0
von Porat 2004 [80]	HR	1	0	0	0	0	1	1	1	0	1	1	1	0
Wang 2004 [81]	HR	1	0	1	0	0	1	0	0	0	1	1	0	0
Wipfler 2011 [28]	HR	0	0	1	1	0	1	1	0	1	1	1	1	0
Wu 2002 [51]	HR	0	0	1	0	0	1	0	0	1	1	1	1	0
Zaffagnini 2011 [29]	HR	1	0	1	1	0	1	1	0	1	1	1	1	0

Abbreviations: HR, high-risk of bias; LR, low-risk of bias; RBA, risk of bias assessment.
The following quality assessment questions were scored as adequate (1), inadequate (0) or not reported (0):

1. A clearly stated aim
2. Inclusion of consecutive patients
3. A description of inclusion and exclusion criteria
4. Inclusion of patients: did the authors report how many eligible patients agreed to participate (i.e. gave consent)?
5. Prospective collection of data. Data were collected according to a protocol established before the beginning of the study.
6. Outcome measure: did they report the OA outcome?
7. Was the used OA classification shown to be valid and reliable?
8. Unbiased assessment of the study outcome and determinants?
9. Were the determinant measures used accurate (valid and reliable)?
10. Follow-up period appropriate to the aim of the study
11. Loss to follow-up: did they report the losses to follow-up? Was the loss to follow-up less than 20%?
12. Adequate statistical analyses: a) correction for confounding; b) there must be a description of the relationship between the determinant and OA outcome or a description of the comparison (with information about the statistical significance); c) reporting variance in the outcome (for example SD, CI))

*Studies were classified as low-risk of bias when they scored adequate (1) on questions 2, 8, 9, 11 and 12a.
Low-risk of bias studies are printed in bold.

CHAPTER 3

Knee Injury and Osteoarthritis Outcome Score or International Knee Documentation Committee Subjective Knee Form: which questionnaire is most useful to monitor patients with an anterior cruciate ligament rupture in the short term?

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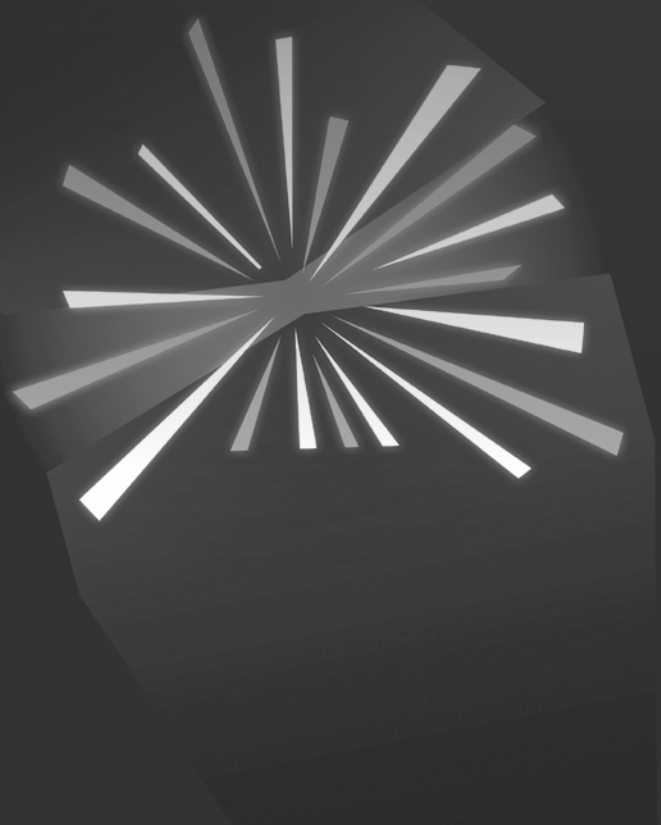

ABSTRACT

Purpose: To evaluate which questionnaire, the Knee Injury and Osteoarthritis Outcome Score (KOOS) or the International Knee Documentation Committee Subjective Knee Form (IKDC subjective), is most useful to evaluate patients with recent anterior cruciate ligament (ACL) ruptures or those within 1 year of an ACL reconstruction.
Methods: Patients with recent (0-6 months) ACL ruptures or those with indications for ACL reconstruction were included. All patients completed the questionnaires shortly after trauma or preoperatively and again 1 year later. The KOOS has 5 subscales, each scored separately. The IKDC subjective consists of one total score. The following measurement properties of the KOOS and IKDC subjective were assessed: content validity (n = 45), construct validity (n = 100), test-retest reliability (n = 50), and responsiveness (n = 50).
Results: Regarding content validity, 2 KOOS subscales (Pain and Activities of Daily Living) were scored as nonrelevant. Two of the 18 questions on the IKDC subjective were assessed as nonrelevant. Only the KOOS subscale Sport and Recreation Function had acceptable construct validity (79% confirmation of the predefined hypotheses). None of the KOOS subscales had a sufficient score for responsiveness (< 75% confirmation of the predefined hypotheses). The IKDC subjective scored acceptable for construct validity (84% confirmation of the predefined hypotheses) and responsiveness (81% confirmation of the predefined hypotheses). All KOOS subscales and the IKDC subjective had a reliability (intraclass correlation coefficient [ICC]) of 0.81 or higher.
Conclusions: The IKDC subjective is more useful than the KOOS questionnaire to evaluate both patients with recent ACL ruptures and those in the first year after ACL reconstruction.
Level of Evidence: Level III, prognostic validation study.

INTRODUCTION

Rupture of the anterior cruciate ligament (ACL) is a common sports-related injury, with an annual incidence of approximately 5 per 10,000 persons in the general population.[1] In the short term, patients can have complaints of instability that influence activities of daily living/sports activity and can cause functional limitations and reduced quality of life (QOL). In the long term, ACL rupture is an injury with an extremely high risk of causing knee osteoarthritis (OA).[2] Therefore, it is important to monitor patients with ACL ruptures over time to evaluate their recovery after conservative or operative treatment so that the rehabilitation program can be adjusted if necessary. Furthermore, monitoring is essential to determine the effectiveness of different interventions during clinical studies. One way to monitor a patient's symptoms and complaints is periodic assessment by the treating physician, including a physical examination that incorporates range of motion and stability tests of the knee. However, it is also important to record the patient's perception of the knee during daily living and sports activities. This can be done using self-administered questionnaires that ask about complaints and symptoms, how the knee functions during daily activities and sports, and QOL. The questions should be relevant for patients with ACL ruptures or reconstructions and should cover the whole domain of symptoms and complaints specific for this group. The questionnaire should also be reliable, i.e., it should evoke similar answers on repeated measurements if the complaints and symptoms do not alter. Finally, if the complaints change over time, the questionnaire should be able to detect these changes (responsiveness). Consequently, the questionnaire that best encompasses these properties will be the most suitable tool to monitor these patients.

Two frequently used questionnaires to monitor patients with ACL injuries are the Knee Injury and Osteoarthritis Outcome Score (KOOS) and the International Knee Documentation Committee Subjective Knee Form (IKDC subjective). Both are intended to measure the same construct and are validated for use in patients with ACL injuries.[3,4] The construct includes symptoms and complaints related to the ACL rupture, as well as limitations in daily life, sports, and leisure. The KOOS was developed to evaluate both short- and long-term consequences of knee injury.[3] The IKDC subjective was designed to detect improvement or deterioration in symptoms, function, and ability to participate in sports activities experienced by patients with a variety of knee problems.[4]

The short-term consequences of an ACL injury differ from the long-term consequences. In our experience, the KOOS is more useful for evaluating the long-term consequences of an ACL rupture (i.e., OA). However, some specific short-term symptoms of an ACL rupture, such as complaints of " giving way," are not included in the KOOS. Because both questionnaires are used interchangeably worldwide to monitor patients

with ACL injuries, there is a need for uniformity during the follow-up of these patients.[5] Therefore, the purpose of this study was to evaluate which questionnaire, the KOOS or the IKDC subjective, is most useful to evaluate patients with recent ACL ruptures or those within 1 year of an ACL reconstruction. We hypothesized that the IKDC subjective is most useful to evaluate short-term consequences of an ACL rupture.

METHODS

The KOOS and IKDC subjective were evaluated on a variety of measurement properties: content validity, construct validity, reliability, and responsiveness.[6] For assessing these properties, a variety of validated questionnaires besides the KOOS and IKDC subjective were used. The questionnaires are described further on.

Population

This study used data from 2 ongoing studies of adult patients with ACL ruptures who visited the orthopaedic surgeon at the outpatient clinic: (1) the KNee osteoArthritis anterior cruciate Ligament Lesion (KNALL) study is a prospective observational study of patients who visited the outpatient clinic within 6 months after trauma. Inclusion criteria were age between 18 and 45 years and the presence of ACL rupture diagnosed by physical examination and magnetic resonance imaging. Patients who did not speak the Dutch language, those with previous ACL injuries or meniscus or cartilage damage, those who had undergone previous surgery of the involved knee, those with disabling comorbidities, and those with radiographic osteoarthritic changes (Kellgren-Lawrence grade > 0) were excluded. The aim of the KNALL study is to evaluate early degenerative changes in the knee after an ACL rupture. (2) Meuffels et al. conducted a prospective randomized clinical trial (RCT) to compare the results of computer-assisted ACL reconstruction with the conventional arthroscopic method.[7] Inclusion criteria were patients with ACL ruptures that were indicated for ACL reconstruction and an age of 18 years and older. Patients who did not speak the Dutch language were excluded. All included patients gave their written informed consent and completed a variety of questionnaires at baseline and at 1-year follow-up.

For this study, we used only patients in the KNALL study and the RCT with complete questionnaires.

Knee Injury and Osteoarthritis Outcome Score

The KOOS is a knee-specific instrument developed to evaluate functioning in daily living, sport, and recreation, as well as the knee-related quality of life in patients with knee injuries who are at risk of OA developing (ACL, meniscus, or chondral injury). This

questionnaire is intended to monitor the short- and long-term consequences (i.e., OA) of these injuries.[3] It has been validated in several populations, e.g., patients undergoing ACL reconstruction[3], total knee arthroplasty[8], and meniscectomy[9]. The Dutch version of the KOOS has been validated in patients with different stages of OA.[10] The KOOS has 5 subscales, each scored separately: Pain (9 items), Symptoms (7 items), Activities of Daily Living (ADL; 17 items), Sport and Recreation Function (Sport/Rec; 5 items) and knee-related Quality of Life (QOL, 4 items). All items are scored 0 to 4; for each subscale the scores are transformed to a 0 to 100 scale (0 representing extreme knee problems and 100 representing no knee problems).[3]

International Knee Documentation Committee Subjective Knee Form

The IKDC subjective is also a knee-specific instrument, developed to measure symptoms, function, and sport activities in patients with a variety of knee problems. The IKDC subjective has been validated in patients who visited orthopaedic sports medicine practices with the preceding injuries.[4] The Dutch version of the IKDC subjective has been validated in patients with a variety of knee-related problems.[11] The questionnaire consists of 18 items and is scored by summing the scores of the individual items (raw score) and then transforming the summed score to a scale ranging from 0 to 100. Higher scores represent lower levels of symptoms and higher levels of function and participation in sports activity.

Short-Form 36

The 36-Item Short Form Health Survey (SF-36) is a generic measure of health status and comprises 8 subscales (Bodily Pain, Physical Functioning, Social Functioning, role limitations because of physical problems [Role-Physical], role limitations because of emotional problems [Role-Emotional], Mental Health, Vitality, and general health perceptions [General Health]). All raw subscale scores are converted to a 0 to 100 scale, in which higher scores indicate higher levels of functioning or wellbeing. The SF-36 has been shown to be reliable and valid in the Dutch general population.[12]

Lysholm Rating Scale

The Lysholm scale was initially designed for physician administration and was validated in patients with ACL injuries and meniscal injuries.[13] It has also been validated as a patient-administered instrument to measure symptoms and function in patients with a variety of knee injuries.[14-17] The Lysholm scale does not measure the domains of functioning in daily activities, sports, and recreational activities. This scale consists of 8 items addressing symptoms and complaints. It is scored on a scale of 0 to 100, with higher scores indicating fewer symptoms and higher levels of functioning.

Visual Analogue Scale for Pain

The 100-mm visual analogue scale (VAS) measures the intensity of pain.[18] Patients are asked to answer the following question: "How much knee pain did you have during the past week?" The higher the score the greater the pain they experienced.

Patient-Rated Improvement for Instability

All patients answered the following question on a 5-point Likert scale at 1-year follow-up: "Have your complaints of knee instability changed, as compared to your first visit at baseline?" The answer options were no complaints anymore, much improved, somewhat improved, neutral, and complaints have increased.

Properties of a questionnaire

The following properties of the KOOS and IKDC subjective were assessed.

1. Are the questions relevant for patients with ACL ruptures? This is an aspect of content validity.[19] For evaluating content validity, we asked experts (orthopaedic surgeons, orthopaedic residents, sport physicians, and physical therapists) in 2 medical centers to score every question in the KOOS and IKDC subjective as relevant or nonrelevant; 19 experts returned the questionnaires. In addition, we asked 26 patients of the KNALL study at baseline for their opinion of the questionnaires. A question was defined as relevant if at least 75% of the patients and experts scored the question as relevant.

2. Does the questionnaire assess the specific symptoms and complaints of a patient with an ACL rupture? Because no gold standard measuring the whole domain of specific symptoms and complaints of an ACL rupture is available, we used construct validity[6]; we compared the KOOS and IKDC subjective with other validated questionnaires or subscales intended to measure the same symptoms and complaints. The construct validity was assessed by comparing the results of the KOOS and the IKDC subjective with a VAS for pain, with the subscales of the SF-36, and with the Lysholm scale. We formulated hypotheses about the expected direction and magnitude of the correlation coefficients between the subscales of the KOOS, the IKDC subjective, and the previously mentioned questionnaires.[6] A panel comprising experts in the field of the questionnaires and ACL injuries (orthopaedic surgeon, specialist in clinimetrics, methodologist, M.D. and Ph.D. candidate), reached consensus about the hypotheses. We defined 2 types of hypotheses (Table 1). Description of these predefined correlation coefficients can be found in Table 1. Section A of Table 1 shows the expected degree of correlation between the questionnaires. In section B, we hypothesized that the correlation coefficients between the KOOS subscales and the IKDC subjective with the 3 physical health subscales of the SF-36 (Physical Functioning, Bodily Pain,

Table 1. Data on construct validity: correlation coefficients between the questionnaires

	n=100	KOOS Pain	KOOS Symptoms	KOOS ADL	KOOS Sport/ Rec	KOOS QOL	IKDC subjective
A	**VAS Pain**						
	Pearson r	***-0.66***	-0.59	-0.58	-0.47	***-0.29***	***-0.48***
	(predefined r)	(≤ - 0.6)	(≥ - 0.4)	(≥ - 0.4)	(≥ - 0.4)	(≥ - 0.4)	(- 0.6 to - 0.4)
	SF-36 physical functioning						
	Pearson r	0.54	0.38	0.55	0.62	0.41	0.67
	(predefined r)	(≤ 0.4)	(0.4 – 0.6)	(≥ 0.6)	(0.4 – 0.6)	(≤ 0.4)	(0.4 – 0.6)
	SF-36 bodily pain						
	Pearson r	***0.62***	0.49	0.56	0.57	***0.36***	0.65
	(predefined r)	(≥ 0.6)	(≤ 0.4)	(≤ 0.4)	(≤ 0.4)	(≤ 0.4)	(0.4 – 0.6)
	Lysholm scale						
	Pearson r	0.68	0.65	0.71	0.61	0.36	***0.62***
	(predefined r)	(≤ 0.4)	(0.4 – 0.6)	(0.4 – 0.6)	(0.4 – 0.6)	(0.4 – 0.6)	(≥ 0.6)
	Confirmed hypotheses A n (%)	2/4 (50%)	0/4 (0%)	0/4 (0%)	0/4 (0%)	2/4 (50%)	2/4 (50%)
B	**Confirmed hypotheses B* n (%)**	11/15 (73%)	14/15 (93%)	10/15 (67%)	15/15 (100%)	11/15 (73%)	14/15 (93%)
	Confirmed hypotheses A + B n (%)	13/19 (68%)	14/19 (74%)	10/19 (53%)	15/19 (79%)	13/19 (68%)	16/19 (84%)

NOTE. Data in parentheses are the determined correlation coefficients of the predefined hypotheses. Construct validity is expressed by the Pearson correlation coefficient. The Pearson correlation coefficient is the calculated correlation between the (subscales of the) questionnaires. Data in bold italic are correlations in agreement with the predefined hypotheses.

Abbreviations: ADL, activities of daily living; IKDC, International Knee Documentation Committee; KOOS, Knee Injury and Osteoarthritis Outcome Score; QOL, quality of life; r, correlation coefficient; SF-36, 36-Item Short Form Health Survey; Sport/Rec, Sport and Recreation Function; VAS, visual analogue scale.

* 15 hypotheses were formulated for all KOOS subscales and IKDC subjective: The correlations with 3 physical health subscales of SF-36 (Physical Functioning, Bodily Pain, Role-Physical) should be at least 0.10 higher than the correlations with 5 mental health subscales of the SF-36 (Mental Health, Vitality, Role-Emotional, Social Functioning, General Health).

Role-Physical) were at least 0.10 higher than the correlation coefficients with the 5 mental health subscales of the SF-36 (Mental Health, Vitality, Role-Emotional, Social Functioning, General Health). In section B, 15 hypotheses for all KOOS subscales and the IKDC subjective were formulated. We considered the construct validity of the KOOS and IKDC subjective to be good if at least 75% of all hypotheses (sections A and B of Table 1 [n = 19]) were confirmed.[19] For evaluating construct validity, we used questionnaires of patients at baseline who had recent ACL trauma or were scheduled for ACL reconstruction because these patients have specific complaints related to their ACL injuries. We used complete baseline questionnaires of 84 patients of the RCT (103 patients were included in total), supplemented to 100 with patient numbers 20 to 33 of the KNALL study (all these patients had complete questionnaires; the first 19 patients of the KNALL study did not have complete questionnaires). In this group, 84 patients were scheduled for ACL reconstruction and 14 patients had acute (0.5 to 3 months previously) ACL rupture.

3. Does the questionnaire provide similar answers on repeated measurements under the assumption that the symptoms and complaints are similar? This is called test-retest reliability.[6] We assessed the measurement error to determine the agreement between repeated measurements in one patient. To distinguish between patients with different degrees of function, despite measurement error, we also determined the reliability. To determine the test-retest reliability, the patients were asked to complete a second questionnaire shortly after completing the baseline or follow-up questionnaire. The average period between completing the first and second questionnaires was 5 days (range, 3 to 12 days). To evaluate whether the symptoms and complaints were similar during this period, we asked the patients if their symptoms and complaints had changed. Patients whose symptoms and complaints had changed during this period were excluded from the analyses (n = 4 patients). For the analyses we used questionnaires of 33 patients of the KNALL study (acute ACL rupture; range from time of trauma to inclusion, 0.5 to 6 months) and questionnaires of 17 patients of the RCT (14 patients preoperatively and 3 patients at 3 months after ACL reconstruction). In total we asked 80 patients to complete the questionnaires twice, and we excluded 30 patients for varying reasons: no completed questionnaires, change of symptoms and complaints between the first and second questionnaires, and less than 3 days or greater than 12 days between the first and second questionnaires.

4. Is the questionnaire able to detect changes over time? This is called responsiveness. Because of lack of a gold standard, the second best option was to compare changes on the KOOS and IKDC subjective with changes on other questionnaires or subscales that measure slightly different constructs.[6] This was assessed by testing predefined

hypotheses about the expected direction and magnitude of the correlation coefficients between the change scores of the questionnaires. The responsiveness was evaluated by comparing the change scores (baseline versus 1 year later) of the KOOS and the IKDC subjective with the change scores of the subscales of the SF-36, the Lysholm scale, the VAS for pain, and the patient-rated improvement (PRI) for instability question. Furthermore, hypotheses about the expected effect size of the KOOS and the IKDC subjective were formulated. The same panel of experts in the field of the questionnaires and ACL injuries reached consensus about the hypotheses. The hypotheses of the relations are described in Table 2. We formulated the same types of hypotheses as for the construct validity. We considered the responsiveness of the KOOS and IKDC subjective to be good if at least 75% of the hypotheses (Table 2, sections A and B [n = 21]) were confirmed.[19] For evaluating responsiveness, patients with a minimum 1-year follow-up were eligible. We used questionnaires of patients who were 1 year past ACL reconstruction and patients who were 1 year past ACL trauma because we assumed that the complaints/symptoms of these patients in 1 year could be changed. In the RCT, we had 47 of 84 patients with complete questionnaires at baseline (just before ACL reconstruction) and at 1-year follow-up. We supplemented this group to 50 with 3 patients of the KNALL study. The baseline questionnaires of these 3 KNALL patients were also used by evaluating construct validity. All 47 patients of the RCT had ACL reconstructions. Two KNALL patients were treated non-operatively during the 1-year follow-up, and 1 KNALL patient was treated operatively.

The presence of floor (minimal score) and ceiling (maximal score) effects at baseline were also evaluated because they can influence the content validity and responsiveness.[19] A floor effect was present with a score between 0 and 5, which represented the poorest score. A ceiling effect was present with a score between 95 and 100, which represented the best possible score. If many patients have the minimal or maximal score, the question might be less relevant and patients cannot improve or deteriorate over time. For assessing floor and ceiling effects, we used the questionnaires of the same 100 patients as used for evaluating construct validity.

Statistical Analysis

Missing data from the KOOS and the IKDC subjective were handled according to the manuals of the questionnaires. If there were one or 2 missing values in the KOOS, they were substituted with the average value for that subscale.[3] If there were one or 2 missing values in the IKDC subjective, they were substituted with the average score of the items that were answered.[4] We excluded patients with more than 2 missing items per subscale in the KOOS and with more than 2 missing items in the IKDC subjective because this level of response was considered invalid and no score could be calculated.

Table 2. Data on responsiveness

	n=50	Δ KOOS Pain	Δ KOOS Symptoms	Δ KOOS ADL	Δ KOOS Sport/Rec	Δ KOOS QOL	Δ IKDC subjective
A	**Δ VAS pain**						
	Pearson r	- 0.49	***- 0.35***	-0.44	- 0.55	***- 0.16***	***- 0.49***
	(predefined r)	(≤ - 0.6)	(≥ - 0.4)	(≥ - 0.4)	(≥ - 0.4)	(≥ - 0.4)	((- 0.6) – (- 0.4))
	Δ SF-36 physical functioning						
	Pearson r	0.58	***0.42***	0.57	0.61	***0.37***	***0.57***
	(predefined r)	(≤ 0.4)	(0.4 – 0.6)	(≥ 0.6)	(0.4 – 0.6)	(≤ 0.4)	(0.4 – 0.6)
	Δ SF-36 bodily pain						
	Pearson r	0.55	***0.31***	0.42	0.49	***0.14***	***0.50***
	(predefined r)	(≥ 0.6)	(≤ 0.4)	(≤ 0.4)	(≤ 0.4)	(≤ 0.4)	(0.4 – 0.6)
	Δ Lysholm scale						
	Pearson r	0.55	***0.51***	***0.50***	0.64	0.39	0.47
	(predefined r)	(≤ 0.4)	(0.4 – 0.6)	(0.4 – 0.6)	(0.4 – 0.6)	(0.4 – 0.6)	(≥ 0.6)
	PRI instability						
	Spearman r	***0.04***	0.15	-0.08	0.14	***0.40***	0.11
	(predefined r)	(≤ 0.4)	(≥ 0.6)	(0.4 – 0.6)	(≥ 0.6)	(0.4-0.6)	(≥ 0.6)
	Effect size* (predefined effect size)	0.60 (≤ 0.2)	0.55 (≥ 0.8)	0.58 (0.2 – 0.5)	0.77 (≥ 0.8)	1.51 (0.2 – 0.5)	***1.36*** (≥ 0.8)
	Confirmed hypotheses A n (%)	1/6 (17%)	4/6 (67%)	1/6 (17%)	0/6 (0%)	4/6 (67%)	4/6 (67%)
B	**Confirmed hypotheses B‡ n (%)**	11/15 = 73%	10/15 = 67%	9/15 = 60%	10/15 = 67%	10/15 = 67%	13/15 = 87%
	Confirmed hypotheses A + B n (%)	12/21 = 57%	14/21 = 67%	10/21 = 48%	10/21 = 48%	14/21 = 67%	17/21 = 81%

NOTE. Δ = change score of baseline and 12 months later. Responsiveness is expressed by Pearson or Spearman correlation coefficient. The Pearson and Spearman correlation coefficient is the calculated correlation between the (subscales of the) questionnaires. Data in parentheses are the determined correlation coefficients of the predefined hypotheses. Data in bold italic are correlations in agreement with the predefined hypotheses.
Abbreviations: ADL, activities of daily living; IKDC, International Knee Documentation Committee; KOOS, Knee Injury and Osteoarthritis Outcome Score; QOL, quality of life; PRI, patient-rated improvement; r, correlation coefficient; SF-36, 36-Item Short Form Health Survey; Sport/Rec, Sport and Recreation Function.
*Mean difference between baseline score and follow-up score/standard deviation at baseline.
‡Fifteen hypotheses were formulated for all change scores of the KOOS subscales and IKDC subjective: the correlations of the change scores of 3 physical health subscales of the SF-36 (Physical Functioning, Bodily Pain, Role-Physical) should be at least 0.10 higher than the correlations of the change scores of 5 mental health subscales of the SF-36 (Mental Health, Vitality, Role-Emotional, Social Functioning, General Health).

Statistical analyses were performed with SPSS Statistics, version 17.0 (SPSS, Chicago, IL). The reliability was assessed by determining the standard error of measurement (SEM) and the smallest detectable change (SDC [individual]) as parameters of measurement error and the intraclass correlation coefficient (ICC) (2-way random effects model, absolute agreement, model [2.1] according to Shrout and Fleiss[20]) as a parameter of reliability. We considered the reliability to be good if the ICC was at least 0.70.[19] To evaluate the construct validity and responsiveness, the Pearson or the Spearman correlation coefficient was calculated. Because of the ordinal scale of the PRI for instability, Spearman correlation coefficients were used to compare the KOOS subscales and the IKDC subjective with the PRI for instability. For the continuous scales, Pearson correlation coefficients were used. To calculate the effect size of the KOOS and the IKDC subjective, the mean change was divided by the standard deviation of the baseline score.[19] Floor and ceiling effects were considered present if more than 15% of the patients achieved the minimal or maximal score.[19] To assess floor and ceiling effects in both questionnaires, we used a range for the minimal (0 to 5) and the maximal (95 to 100) sores.

RESULTS

Table 3 presents the characteristics of the study population. The construct validity and the floor and ceiling effects were determined in 100 patients. The responsiveness was assessed in a subgroup of 50 patients for whom 1-year follow-up data were available. The reliability was assessed in another group of 50 patients.

Relevance of the questions

Five of the 9 questions (56%) of the KOOS subscale Pain were rated as relevant. Four questions were rated as nonrelevant: P5, P7, P8, and P9 (see Appendix for the KOOS and IKDC subjective). In the ADL subscale, only 5 of the 17 questions (29%) were rated as relevant; questions A3, A4, A6, A8, A9, A10, A11, A12, A13, A14, A15, and A17 were rated as nonrelevant. The KOOS subscales Symptoms (86%), Sport/Rec (100%), and QOL (100%), and the IKDC subjective (89%) had a high percentage of relevant items (Table 4). Question S7 (KOOS Symptoms) and questions Sp4 and Sp6 of the IKDC subjective were rated as nonrelevant.

Minimal and maximal scores

No floor effects (minimal scores) were found in the 2 questionnaires. Ceiling effects (maximal scores) were found on the KOOS subscales Pain (20%) and ADL (46%). None of the patients scored the maximal score of the IKDC subjective (Table 4).

Table 3. Baseline characteristics of the study population

	Construct Validity (n = 100)	Responsiveness (n = 50)	Reliability (n = 50)
Age (yr), mean (range)	26 (18-57)	28 (18-46)	27 (18-48)
Sex	25	24	40
Women (%)			
KOOS*			
Pain	83.3 (27.8-100.0)	80.6 (47.2-100.0)	75.0 (36.1-100.0)
Symptoms	73.2 (25.0-92.9)	73.2 (35.7-92.9)	62.5 (28.6-100.0)
ADL	94.1 (17.7-100.0)	94.1 (35.3-100.0)	87.5 (32.4-100.0)
Sport/Rec	50.0 (0.0-100.0)	60.0 (0.0-100.0)	30.0 (0.0-90.0)
QOL	37.5 (6.3-81.3)	37.5 (6.3-75.0)	37.5 (0.0-93.8)
IKDC subjective*	63.8 (26.4- 93.1)	69.5 (31.0-93.1)	59.2 (24.1-97.7)
Tegner activity scale before trauma†	9 (1-10)	9 (1-10)	9 (3-10)
Tegner activity scale baseline†	3 (0-10)	4 (0-10)	3 (0-6)

NOTE. Data are presented as median (minimum-maximum).

Abbreviations: ADL, activities of daily living; IKDC, International Knee Documentation Committee; KOOS, Knee Injury and Osteoarthritis Outcome Score; QOL, quality of life; Sport/Rec, Sport and Recreation Function.

*Range, 0-100 (0, extreme knee problems; 100, no knee problems)

†Range, 0-10 (0, sick leave or disability pension because of knee problems; 10, competitive sports, soccer national and international elite).

Reliability

Both questionnaires had ICCs of 0.81 or higher. The standard error of the mean of the KOOS subscales ranged from 6.6 to 12.7, and the standard error of the mean of the IKDC subjective was 4.4. The SDC (individual) of the KOOS subscales ranged from 18.3 to 35.2, and the SDC (individual) of the IKDC subjective was 12.2 (Table 4).

Assessment of specific symptoms and complaints of patients with ACL injuries (construct validity)

Only for the KOOS subscale Sport/Rec and the IKDC subjective did more than 75% of the results agree with our hypotheses (Table 1).

Ability to measure changes over time (responsiveness)

Table 2 shows the results of the responsiveness analyses. Only the IKDC subjective achieved the criterion that 75% or more of all hypotheses (Table 2 , Sections A and B) should be confirmed. For the IKDC subjective, 81% of the hypotheses were confirmed.

Table 4. Data on content validity, floor and ceiling effects, and reliability

	Content Validity* n=45	**Floor & Ceiling Effects† Baseline n = 100**		**Reliability n = 50**		
				test-retest	**Measurement error**	
	N Relevant/Total (% Relevant)	Lowest Score 0-5%	Highest Score 95-100%	ICC Agreement (95% CI)	SEM	SDC (Individual)
KOOS						
Pain	5/9 (56)	0	20	0.87 (0.78-0.92)	6.6	18.3
Symptoms	6/7 (86)	0	0	0.81 (0.56-0.91)	9.1	25.2
ADL	5/17 (29)	0	46	0.85 (0.75-0.91)	7.8	21.6
Sport/Rec	5/5 (100)	11	5	0.81 (0.64-0.89)	12.7	35.2
QOL	4/4 (100)	0	0	0.83 (0.72-0.90)	7.6	21.1
IKDC subjective	16/18 (89)	0	0	0.93 (0.89-0.96)	4.4	12.2

Abbreviations: ADL, activities of daily living; CI, confidence interval; ICC agreement, intraclass correlation coefficient for agreement; IKDC, International Knee Documentation Committee; KOOS, Knee Injury and Osteoarthritis Outcome Score; QOL, quality of life; SDC; smallest detectable change; SEM, standard error of measurement,

*Content validity is expressed by number of relevant items divided by total items; between parentheses are the percentages of relevant items presented. An item is scored as relevant if 75% of the experts and patients scored it as relevant. Twenty-six patients and 19 experts (in total 45) assessed the content validity.

†Floor & Ceiling effects, baseline, are presented as the percentage (%) of patients who scored the lowest score (range, 0-5) and the highest score (range, 95-100).

DISCUSSION

The results show that the KOOS did not perform optimally on the following properties: relevance of the questions, construct validity, responsiveness, and ceiling effects. In contrast, the IKDC subjective satisfied the criteria for all properties in this specific group of patients.

We did not evaluate the Lysholm rating scale because this questionnaire measures mainly function of the knee and not the patient' s perception of functioning in daily activities, sports, and recreational activities.

The KOOS subscales Pain and ADL were scored as not relevant for this specific group of patients on the short-term follow-up. Roos et al.[3] assessed the relevance of the questions for patients with both short- and long-term symptoms or functional disabilities resulting from meniscus or ACL injuries. However, no studies have investigated the monitoring of short-term symptoms in patients with ACL ruptures. The high percentage of the maximal score at baseline found for the KOOS subscales Pain and ADL suggests that the questions were not relevant and/or specific for patients with ACL

injuries. In the validation study of the Swedish version of the KOOS[21], these 2 subscales also had ceiling effects (Pain, 2.5%; ADL, 3.2%), but they were not as high as those we found. It is worth emphasizing that instead of taking 0 as the minimal score and 100 as the maximal score, we defined a range of 0 to 5 as the minimal score and 95 to 100 as the maximal score. Minimal scores at baseline, after trauma, or preoperatively are less important because it is expected that patients with ACL injuries will improve over time. The IKDC subjective showed good content validity, which was also found in the Dutch validation study of Haverkamp et al.[11] Consequently, we concluded that unlike the other 3 subscales and the IKDC subjective, the KOOS subscales Pain and ADL are not relevant for measuring function, symptoms, and complaints in patients with ACL injuries in the short-term. Our results of the content validity confirm the results of the study of Hambly et al.[22], but they investigated only this aspect of the measurement properties.

To evaluate the ability of the questionnaires to assess the specific symptoms and complaints of a patient with an ACL rupture, we tested hypotheses about the magnitude and direction of the relations between the subscales of the questionnaires. Only the KOOS subscale Sport/Rec and the IKDC subjective met the criterion of confirming at least 75% of the predefined hypotheses. In other studies, construct validity was also assessed by correlating questionnaires, but no specific hypotheses were defined.[3,11] Without specific hypotheses there is a risk of bias, because it is tempting to formulate explanations for the low and high correlation coefficients retrospectively instead of concluding that the questionnaire may not be valid.[6] Conversely, the choice of magnitude of the hypotheses is arbitrary.

To assess whether the questionnaires are able to detect changes over time, we used the same procedure, i.e., testing predefined hypotheses. Only the IKDC subjective achieved the criterion that 75% or more of all hypotheses should be confirmed. In the study of Roos et al.[3], the effect size 6 months postoperatively is reported without mentioning the expected effect size. In that study, only the results of 2 subscales, Symptoms and Sport/Rec, agreed with our predefined hypotheses about the expected magnitude of the effect size. As we expected, our study showed a large effect size (1.36) of the IKDC subjective. A large effect size means a bigger detectable difference between the baseline and follow-up measurements. Responsiveness of the IKDC subjective was not investigated in the development and validation study of Irrgang et al.[4] or in the Dutch validation study of Haverkamp et al.[11] A disadvantage of the IKDC subjective is the use of one total score, which means it is impossible to see in which domain (e.g., symptoms, function, or sports activities) the patients have improved. According to our results, the IKDC subjective is more responsive to changes over time than is the KOOS.

A strength of this study was that the participants were representative of patients with recent ACL ruptures and of patients scheduled for ACL reconstruction. Our population comprised the whole domain of patients with ACL injuries: acutely injured patients, patients with chronic instability, patients treated conservatively or operatively, and young and old patients. The patients in our study had a pretrauma median Tegner activity level of 9 (range, 1 to 10), which is similar to the levels of patients with ACL injuries in other studies.[23,24] The activity level of our study population was high; however, most patients with ACL injuries are young and physically active.[25] Besides, patients with complaints who visit an orthopaedic surgeon or sports physician are perhaps the more active patients. Our population was a reflection of patients with ACL injuries who visit an orthopaedic or sports medicine outpatient clinic. We analyzed if patient sex had an effect on the scores and we found no significant difference on the KOOS and IKDC subjective scores between men and women; hence, we did not add these results. In contrast, the study of Ageberg et al.[26] found that female patients reported statistically significant worse outcomes than did male patients before and at 1 and 2 years after ACL reconstruction.

Another strength is assessment of the measurement properties of both questionnaires in the population of interest, i.e., patients with ACL injuries evaluated in the short term. Other validation studies of the KOOS and IKDC subjective investigated more heterogeneous populations, e.g., patients with OA and patients with meniscus, cartilage, and other ligament injuries.[4,10,11,21] Yet another advantage is that we used clearly defined criteria to assess the properties and had a large sample size to test the hypotheses.

The KOOS is a reliable questionnaire for evaluating knee OA and the long-term consequences of an ACL rupture or reconstruction because it includes aspects that are important for OA.[3,10] Based on these studies and on the results of the present study, we recommend that all patients with ACL injuries be asked to complete the IKDC subjective and KOOS at the first visit. To monitor the patient' s perception of recovery during the first year, we recommend using the IKDC subjective.

Limitations

This study also has some limitations. First, defining the hypotheses remains arbitrary. To avoid this, we used a transparent method and clearly defined hypotheses. A strong point was the use of predefined hypotheses about the magnitude and direction of the correlation coefficients. This was done to prevent alternative explanations about unexpected correlation coefficients instead of concluding that the property did not meet the criteria. Second, for assessment of the construct validity and responsiveness, all the hypotheses were equally important. In other words, all hypotheses counted equally for

the overall assessment that 75% or more of all hypotheses should be confirmed. To date there has been no consensus or guideline about the number of hypotheses that should be tested and confirmed or about weighted testing of the hypotheses.

CONCLUSIONS

The IKDC subjective is more useful than the KOOS questionnaire to evaluate patients with recent ACL ruptures and patients in the first year after ACL reconstruction.

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APPENDIX 1

KOOS KNEE SURVEY

Today's date:
Date of birth:
Name:

Instructions: This survey asks for your view about your knee. This information will help us keep track of how you feel about your knee and how well you are able to perform your usual activities.
Answer every question by ticking the appropriate box, only one box for each question. If you are unsure about how to answer a question, please give the best answer you can.

Symptoms
These questions should be answered thinking of your knee symptoms during the **last week**.

S1. Do you have swelling in your knee?

Never	Rarely	Sometimes	Often	Always
☐	☐	☐	☐	☐

S2. Do you feel grinding, hear clicking or any other type of noise when your knee moves?

Never	Rarely	Sometimes	Often	Always
☐	☐	☐	☐	☐

S3. Does your knee catch or hang up when moving?

Never	Rarely	Sometimes	Often	Always
☐	☐	☐	☐	☐

S4. Can you straighten your knee fully?

Always	Often	Sometimes	Rarely	Never
☐	☐	☐	☐	☐

S5. Can you bend your knee fully?

Always	Often	Sometimes	Rarely	Never
☐	☐	☐	☐	☐

Stiffness
The following questions concern the amount of joint stiffness you have experienced during the **last week** in your knee. Stiffness is a sensation of restriction or slowness in the ease with which you move your knee joint.

S6. How severe is your knee joint stiffness after first wakening in the morning?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

S7. How severe is your knee stiffness after sitting, lying or resting **later in the day**?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Pain

P1. How often do you experience knee pain?

Never	Monthly	Weekly	Daily	Always
☐	☐	☐	☐	☐

What amount of knee pain have you experienced the last week during the following activities?

P2. Twisting/ pivoting on your knee

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P3. Straightening knee fully

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P4. Bending knee fully

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P5. Walking on flat surface

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P6. Going up or down stairs

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P7. At night while in bed

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P8. Sitting or lying

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P9. Standing upright

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Function, daily living

The following questions concern your physical function. By this we mean your ability to move around and to look after yourself. For each of the following activities please indicate the degree of difficulty you have experienced in the **last week** due to your knee.

A1. Descending stairs

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A2. Ascending stairs

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

For each of the following activities please indicate the degree of difficulty you have experienced in the **last week** due to your knee.

A3. Rising from sitting

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A4. Standing

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A5. Bending to floor/ pick up an object

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A6. Walking on flat surface

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A7. Getting in/ out of car

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A8. Going shopping

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A9. Putting on socks/ stockings

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A10. Rising from bed

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A11. Taking off socks/ stockings

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A12. Lying in bed (turning over, maintaining knee position)

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A13. Getting in/ out of bath

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A14. Sitting

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A15. Getting on/ off toilet

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

For each of the following activities please indicate the degree of difficulty you have experienced in the **last week** due to your knee.

A16. Heavy domestic duties (moving heavy boxes, scrubbing floors, etc)

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A17. Light domestic duties (cooking, dusting, etc)

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Function, sports and recreational activities

The following questions concern your physical function when being active on a higher level. The questions should be answered thinking of what degree of difficulty you have experienced during the **last week** due to your knee.

SP1. Squatting

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

SP2. Running

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

SP3. Jumping

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

SP4. Twisting/ pivoting on your inured knee

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

SP5. Kneeling

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Quality of life

Q1. How often are your aware of your knee problem?

Never	Monthly	Weekly	Daily	Constantly
☐	☐	☐	☐	☐

Q2. Have you modified your life style to avoid potentially damaging activities to your knee?

Not at all	Mildly	Moderately	Severely	Totally
☐	☐	☐	☐	☐

Q3. How much are you troubled with lack of confidence in your knee?

Not at all	Mildly	Moderately	Severely	Extremely
☐	☐	☐	☐	☐

Q4. In general, how much difficulty do you have with your knee?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Thank you very much for completing all the questions in this questionnaire.

APPENDIX 2

2000 IKDC Subjective Knee Evaluation Form

Your full Name:

Today's Date: Date of Injury:

Symptoms*:

*Grade symptoms at the highest activity level at which you think you could function without significant symptoms, even if you are not actually performing activities at this level.

1. What is the highest level of activity that you can perform without significant knee pain?
   - ☐Very strenuous activities like jumping or pivoting as in basketball or soccer
   - ☐Strenuous activities like heavy physical work, skiing or tennis
   - ☐Moderate activities like moderate physical work, running or jogging
   - ☐Light activities like walking, housework or yard work
   - ☐Unable to perform any of the above activities due to knee pain

2. During the past 4 weeks, or since your injury, how often have you had pain?

	0	1	2	3	4	5	6	7	8	9	10	
Never	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	Constant

3. If you have pain, how severe is it?

	0	1	2	3	4	5	6	7	8	9	10	
No pain	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	Worst pain imaginable

4. During the past 4 weeks, or since your injury, how stiff or swollen was your knee?
   - ☐Not at all
   - ☐Mildly
   - ☐Moderately
   - ☐Very
   - ☐Extremely

5. What is the highest level of activity you can perform without significant swelling in your knee?
   ❑Very strenuous activities like jumping or pivoting as in basketball or soccer
   ❑Strenuous activities like heavy physical work, skiing or tennis
   ❑Moderate activities like moderate physical work, running or jogging
   ❑Light activities like walking, housework or yard work
   ❑Unable to perform any of the above activities due to knee swelling

6. During the <u>past 4 weeks</u>, or since your injury, did your knee lock or catch?

   ❑ Yes ❑ No

7. What is the highest level of activity you can perform without significant giving way in your knee?
   ❑Very strenuous activities like jumping or pivoting as in basketball or soccer
   ❑Strenuous activities like heavy physical work, skiing or tennis
   ❑Moderate activities like moderate physical work, running or jogging
   ❑Light activities like walking, housework or yard work
   ❑Unable to perform any of the above activities due to giving way of the knee

<u>Sports Activities:</u>

8. What is the highest level of activity you can participate in on a regular basis?
   ❑Very strenuous activities like jumping or pivoting as in basketball or soccer
   ❑Strenuous activities like heavy physical work, skiing or tennis
   ❑Moderate activities like moderate physical work, running or jogging
   ❑Light activities like walking, housework or yard work
   ❑Unable to perform any of the above activities due to knee

9. How does your knee affect your ability to:

		Not difficult at all	Minimally difficult	Moderately difficult	Extremely difficult	Unable to do
a.	Go up stairs	❑	❑	❑	❑	❑
b.	Go down stairs	❑	❑	❑	❑	❑
c.	Kneel on the front of your knee	❑	❑	❑	❑	❑
d.	Squat	❑	❑	❑	❑	❑
e.	Sit with your knee bent	❑	❑	❑	❑	❑

f.	Rise from a chair	☐	☐	☐	☐	☐
g.	Run straight ahead	☐	☐	☐	☐	☐
h.	Jump and land on your involved leg	☐	☐	☐	☐	☐
i.	Stop and start quickly	☐	☐	☐	☐	☐

Function

10 How would your rate the function of your knee on a scale of 0 to 10 with 10 being normal, excellent function and 0 being the inability to perform any of your usual daily activities which may include sports?

FUNCTION PRIOR TO YOUR KNEE INJURY:

	0	1	2	3	4	5	6	7	8	9	10	
Cannot perform daily activities	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	No limitation in daily activities

CURRENT FUNCTION OF YOUR KNEE:

	0	1	2	3	4	5	6	7	8	9	10	
Cannot perform daily activities	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	No limitation in daily activities

CHAPTER 4

Are magnetic resonance imaging recovery and laxity improvement possible after anterior cruciate ligament rupture in non-operative treatment?

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ABSTRACT

Purpose: This study aimed to determine whether anterior cruciate ligament (ACL) features on magnetic resonance imaging (MRI) and knee laxity are improved 2 years after ACL rupture treated non-operatively and to analyze the relation between changes in scores of ACL features and changes in laxity.

Methods: One hundred fifty-four eligible patients were included in a prospective multicenter cohort study with two 2-year follow-up. Inclusion criteria were (1) ACL rupture diagnosed by physical examination and MRI, (2) MRI within 6 months after trauma, and (3) age 18 to 45 years. Laxity tests and MRI were performed at baseline and at 2-year follow-up. Fifty of 143 patients, for whom all MRI data was available, were treated non-operatively and were included for this study. Nine ACL features were scored using MRI: fiber continuity, signal intensity, slope of ACL with respect to the Blumensaat line, distance between the Blumensaat line and the ACL, tension, thickness, clear boundaries, assessment of original insertions, and assessment of the intercondylar notch. A total score was determined by summing scores for each feature.

Results: Fiber continuity improved in 30 patients (60%), and the empty intercondylar notch resolved for 22 patients (44%). Improvement in other ACL features ranged from 4% to 28%. Sixteen patients (32%) improved on the Lachman test (change from soft to firm end points [n=14]; decreased anterior translation [n=2]), one patient (2%) showed improvement with the KT-1000 arthrometer (MEDmetric, San Diego, CA) and four patients (8%) improved on the pivot shift test. Improvement on the Lachman test was moderately negatively associated with total score of ACL features at follow-up. Analyzing ACL features separately showed that only signal intensity improvement, clear boundaries and intercondylar notch assessment were positively associated with improvement on the Lachman test.

Conclusion: Two years after ACL rupture and non-operative management, patients experienced partial recovery on MRI, and some knee laxity improvement was present. Improvement of ACL features on MRI correlates moderately with improved laxity.

Level of evidence: Level II, Prospective comparative study

INTRODUCTION

Anterior cruciate ligament (ACL) rupture is a common sports-related injury, occurring in 5 per 10,000 persons annually.[1] An experienced clinician can diagnose ACL rupture by medical history and physical examination.[2,3] Magnetic resonance imaging (MRI) is an accurate, noninvasive method used to evaluate intra-articular knee injuries and is useful in cases of diagnostic uncertainty or concomitant injury and for research.[4] Two systematic reviews report MRI sensitivities of 86% and 94%, and specificities of 95% and 94%, for diagnosing ACL injuries.[5,6]

The ACL is an intra-articular ligament with limited healing capacity. Unlike the medial collateral ligament, there is no formation of functional scar tissue or increased histologic blood flow during recovery. It appears that after ACL rupture, a layer of synovial tissue surrounds the ruptured ends; cells in this synovial tissue may retract tissue and limit healing.[7-9] This limited healing capacity has been clinically demonstrated as abnormal laxity and high revision rates after initial ACL suturing.[10,11]

Current treatment options are surgical reconstruction of the ACL or non-operative treatment with rehabilitation. If initial knee instability exists, operative treatment is chosen; otherwise, non-operative treatment is indicated. However, the decision between operative and non-operative treatment can be complex and is also influenced by different variables, e.g., the patient's activity, willingness to modify activities, age, and additional injuries.

In this study, we reviewed non-operatively treated patients because we were interested in the capability of the ACL to recover after rupture, expressed by changes in laxity seen with phisical examination, and the possibility of confirming recovery on MRI of the ACL. Gereats et al.[3] showed that experience in diagnosing ACL rupture is an important factor for performing laxity tests with accuracy. If changes in laxity are related to changes in ACL features on MRI, the latter can support the interpretation of the ACL physical examination.

Radiographic studies of ACL recovery show improvement on MRI.[12-18] In addition to improved MRI signs, some studies show improved knee stability.[14-17] However, these latter studies had small sample sizes and reported MRI improvements in aggregate rather than as individual MRI sign improvements. Some researchers have reported no correlation between radiographic ACL recovery and clinical knee stability.[13,18]

The aim of this study was to determine whether ACL features on MRI and knee laxity are improved 2 years after ACL rupture treated non-operatively and to analyze the relation between changes in scores of ACL features and changes in laxity. We hypothesized that ACL features on MRI would improve during follow-up and that changes in scores of ACL features are related to changes in laxity.

METHODS

Between January 2009 and November 2010, 154 eligible patients were included in the KNee osteoArthritis anterior cruciate Ligament Lesion (KNALL) study - a prospective multicenter cohort study with 2 years of follow-up. The patients were recruited from 3 hospitals in the Netherlands: Erasmus MC University Medical Center, Rotterdam; Medical Center Haaglanden, the Hague; and Reinier de Graaf Gasthuis, Delft. Inclusion criteria were (1) ACL rupture diagnosed by physical examination and MRI, (2) MRI within 6 months after trauma, and (3) age 18 to 45 years. Patients who did not speak Dutch, those with previous intra-articular knee trauma or surgery of the involved knee, those with disabling comorbidities, and those with osteoarthritic changes on radiography (Kellgren and Lawrence grade > 0) were excluded.

Baseline and 2-year follow-up MRI data were available for 143 patients. All patients were treated according to the Dutch guideline on ACL injury.[4] Of the 143 patients, 50 patients were treated non-operatively during the 2-year follow-up period. Two of the 50 patients treated non-operatively had medial meniscectomies during the 2-year follow-up period. At the time of inclusion, 10 patients had 1+ medial collateral ligament injury and 7 patients lateral collateral ligament injury (1+, n = 4, ≥ 2+, n = 3). Patients were treated only with a brace if a collateral ligament injury was present. All patients had physiotherapy according to the Dutch guidelines for physical therapists. Our institution's Medical Ethics Committee approved the study, and all included patients gave their written informed consent and were evaluated at baseline, at 1 year, and at 2 years.

At baseline, MR images were obtained using MRI scanners with a magnetic field strength of 1.0 (n = 7), 1.5 (n = 37) or 3.0 (n = 6) Tesla. At follow-up, all MR images were acquired on the same type scanner with a magnetic field strength of 1.5 Tesla MRI. Patients' legs were positioned neutrally. All MRI examinations included a set of routine clinical MRI pulse sequences. To assess ACL features, we used sagittal and coronal proton density weighted turbo spin echo (TSE) sequences (slice thickness 3 mm, repetition time (TR)/echo time (TE), 2700/27 ms) and the coronal T2-weighted TSE sequence with fat saturation (slice thickness 3 mm, TR/TE: 5030/71 ms).

Measurements

An expert panel, consisting of an orthopaedic surgeon experienced in ACL pathologic conditions, an experienced musculoskeletal radiologist, and a physician researcher, defined 9 features by which to assess the ACL on MRI, based on primary MRI signs.[19] Features (Figs 1-7) were scored as normal (0) or abnormal (1), except for fiber continuity, which was scored as intact (0), partially visible (1), or no distinct fibers visible (2):

- Fiber continuity (0 = intact; 1 = partially visible; 2 = no distinct fibers visible)
- Signal intensity (abnormal = high or heterogeneous signal)
- Slope of ACL with respect to the Blumensaat line (abnormal = more horizontal orientation)
- Distance between the Blumensaat line and ACL (abnormal = increased distance)
- Tension (abnormal = bowing)
- Thickness (abnormal = thickening)
- Clear boundaries (abnormal = unclear boundaries)
- Assessment of original insertions (abnormal = ACL tissue outside original insertions)
- Assessment of intercondylar notch (abnormal = empty notch)

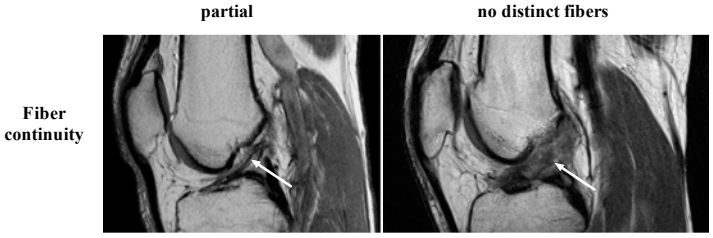

Figure 1. Fiber continuity (arrows: partially visible; no distinct fibers visible). MRI sequence: sagittal proton density weighted turbo spin echo (TSE); slice thickness, 3 mm; repetition time (TR)/time echo (TE), 2700/27 ms.

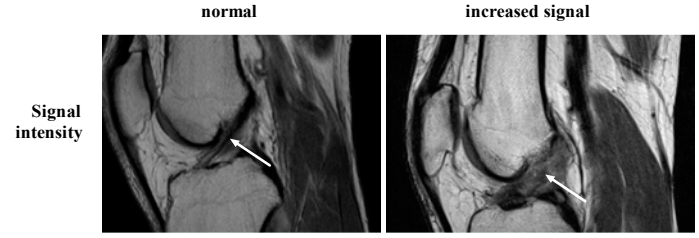

Figure 2. Signal intensity (abnormal = high or heterogeneous signal). MRI sequence: sagittal proton density weighted turbo spin echo (TSE); slice thickness, 3 mm; repetition time (TR)/time echo (TE), 2700/27 ms.

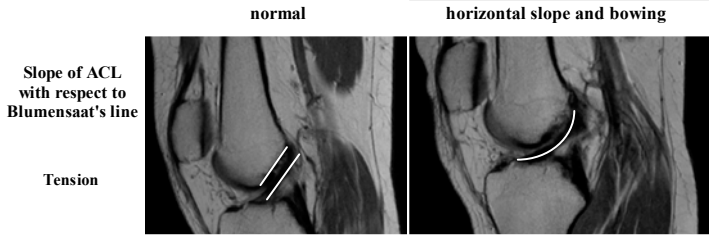

Figure 3. Slope of anterior cruciate ligament (ACL) with respect to Blumensaat line and tension (abnormal = more horizontal orientation and bowing). MRI sequence: sagittal proton density weighted turbo spin echo (TSE); slice thickness, 3 mm; repetition time (TR)/time echo (TE), 2700/27 ms.

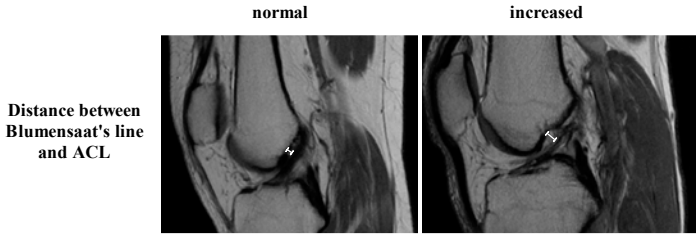

Figure 4. Distance between Blumensaat line and anterior cruciate ligament (ACL) (abnormal = increased distance). MRI sequence: sagittal proton density weighted turbo spin echo (TSE); slice thickness, 3 mm; repetition time (TR)/time echo (TE), 2700/27 ms.

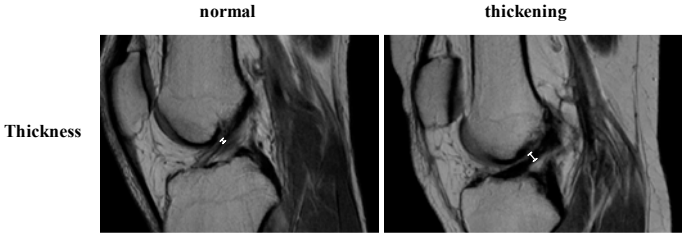

Figure 5. Thickness (abnormal = thickening). MRI sequence: sagittal proton density weighted turbo spin echo (TSE); slice thickness, 3 mm; repetition time (TR)/time echo (TE), 2700/27 ms.

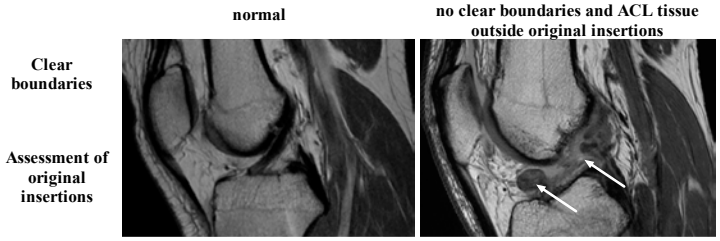

Figure 6. Clear boundaries and assessment of original insertions (abnormal = unclear boundaries and anterior cruciate ligament [ACL] tissue outside original insertions). MRI sequence: sagittal proton density weighted turbo spin echo (TSE); slice thickness, 3 mm; repetition time (TR)/time echo (TE), 2700/27 ms.

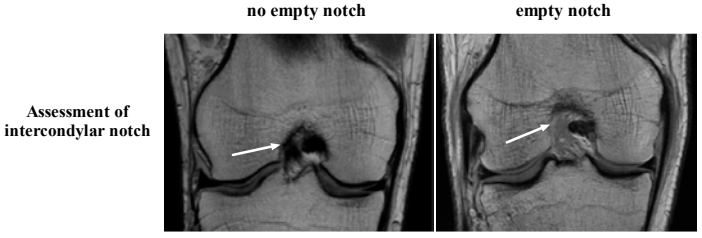

Figure 7. Assessment of intercondylar notch (arrow) (abnormal = empty notch). MRI sequence: coronal proton density weighted turbo spin echo (TSE); slice thickness, 3 mm; repetition time (TR)/time echo (TE), 2700/27 ms.

A total score was determined by summing scores for these 9 features. A score of 10 was maximally abnormal for all features, whereas a score of 0 was normal for all features.

Before the application of this scoring method we organized training sessions with the expert panel. We made an atlas of examples of all ACL features with their normal and abnormal scores. Additionally, we scored several knee MRIs and discussed discrepancies in scoring until consensus was reached. A physician researcher blinded to clinical history evaluated all MR images. Baseline and follow-up MR images were assessed contemporaneously; the order of measurements was known. Laxity tests - including Lachman test, KT-1000 arthrometer (MEDmetric, San Diego, CA) measurements, and the pivot shift test - were performed at baseline and at follow-up. The Lachman test was performed as described by Torg et al.[20] to assess tibial translation. Using the International Knee Documentation Committee form, the translation was scored as 0 (-1 to 2 mm), 1+ (> 2 to 5 mm), 2+ (> 5 to 10 mm), or 3+ (> 10 mm), and the end point was scored as soft or firm.[21] Instrumented anterior laxity testing of the knee was performed using the KT-1000 arthrometer.[22,23] We used absolute maximal measurement values for analysis because some patients had a history of ACL injury in the contralateral knee. Rotational instability was evaluated using the pivot shift test,[24] which was scored as normal (0), glide (1+), clunk (2+) or gross (3+) according to the International Knee Documentation Committee.[21] The same physician examined all patients at baseline and at follow-up. At baseline, the physician evaluator was aware of the presence of ACL rupture on MRI but unaware of the scores of the ACL features. At follow-up, the physician examined patients without knowledge of MRI findings. Baseline MRI assessments and laxity tests were compared with measurements at 2 years.

Definition of improvement and deterioration

Improvement of ACL features on MRI was defined as a score changed from 1 to 0 (or from 2 to 1 for fiber continuity). Deterioration was defined as present if a score of an ACL feature on MRI changed from 0 to 1 at 2 years (or from 0 to 2 or 1 to 2 for fiber continuity).

Laxity improvement was determined separately for each test. The Lachman test result was improved at follow-up if the anterior translation changed to 0, by an improvement of 2 or more, or if the end point changed from soft to firm. Laxity deterioration was present if the anterior translation increased to 1+ or greater and the end point did not improve. Pivot shift test improvement at follow-up was defined as a change to 0 or 2-step improvement (e.g., from 3+ to 1+). Pivot shift test deterioration was defined as an increase of 1+ or greater. KT-1000 arthrometer laxity was improved at follow-up if there was a difference of at least 4 mm of the absolute maximal value compared with

baseline. An increase of at least 4 mm was defined as laxity deterioration by KT-1000 arthrometer measurements.

Reliability

To assess inter-rater reliability of ACL scoring on MRI, an orthopedic surgeon and a physician researcher, both with experience in ACL injuries, independently scored the same 25 MRIs.

Statistical Analysis

Descriptive statistics were used to analyze baseline characteristics. Mean and standard deviation (SD) were obtained for normally distributed variables. Median and inter-quartile range (IQR) were obtained for non-normally distributed variables. To assess inter-rater reliability of ACL scores, we determined the prevalence-adjusted bias-adjusted kappa (PABAK), which considers both the prevalence of positive findings and bias of each observer to report positive findings.[25] A kappa value of greater than 0.8 is considered very good, between 0.6 and 0.8 is good, between 0.4 and 0.6 is moderate, and a kappa less than 0.4 indicated fair agreement.[26,27] Prevalence of abnormal scores of the ACL features on MRI at baseline and at 2 years are reported as percentages. Percentages of improvement of ACL features and laxity were determined by using the previously described improvement definition. The relation between improvement on laxity and ACL features on MRI was analyzed using binary logistic regression. $P < .05$ was considered statistically significant.

RESULTS

Baseline patient characteristics (n = 50) are presented in Table 1. The mean age at trauma was 29.9 (SD 7.0) years, and 34% of patients were women. At baseline, all patients had a positive Lachman test (at least 1+), and 84% had a soft end point. The mean maximal anterior translation, measured by KT-1000 arthrometer, was 11.3 (SD 2.1) mm and 42% had a positive pivot shift test result.

Most ACL features showed good to very good inter-rater reliability, with PABAK values ranging from 0.68 to 1. Inter-rater reliability for "thickness" had a PABAK value of 0.44.

Prevalence of abnormal scores for ACL features on MRI at baseline and at 2 years is presented in Table 2. Abnormal scores for ACL features ranged from 66% to 100% at baseline and from 28% to 94% at 2 years. The median total score of ACL features changed from 10 (IQR: 8-10) at baseline to 7 (IQR: 5-9) at the 2-year follow-up.

Table 1. Baseline characteristics

Characteristics	n = 50
Age (years), mean (SD)	29.9 (±7.0)
Female sex, n (%)	17 (34)
BMI (kg/m²), median (IQR)	24.3 (22.4-27.1)
Time from trauma to baseline MRI in months, median (IQR)	1.1 (0.5-2.4)
Activity (Tegner score), median (IQR)	
Before trauma	8.0 (7.0-9.0)
At baseline	3.0 (2.0-4.0)
Lachman test, n (%)	
Normal	0
1+	16 (32)
2+	33 (66)
3+	1 (2)
Lachman test; soft end point, n (%)	42 (84)
Pivot shift test, n (%)	
Normal	22 (44)
Glide	18 (36)
Clunk	3 (6)
Not applicable*	7 (14)
KT-1000 arthrometer (n = 49) †	
Maximal manual in mm, mean (SD)	11.3 (2.1)

BMI, body mass index; IQR, interquartile range; SD, standard deviation
*Not applicable because of opposing muscle contraction.
†Missing data for one patient because of large leg circumference.

Table 2. ACL features on MRI at baseline and at 2-year follow-up (n = 50)

ACL Features	T0 Abnormal Score n (%)	T2 Abnormal Score n (%)
Fiber continuity	47 (94)	38 (76)
Partially visible	8 (16)	23 (46)
No distinct fibers	39 (78)	15 (30)
Signal intensity	48 (96)	42 (84)
Slope	46 (92)	42 (84)
Distance of Blumensaat to ACL	50 (100)	41 (82)
Tension	47 (94)	47 (94)
Thickness of ACL	50 (100)	43 (86)
Clear boundaries	47 (94)	34 (68)
Assessment of original insertions	33 (66)	21 (42)
Assessment of intercondylar notch	36 (72)	14 (28)
Total score, median (IQR)	10 (8-10)	7 (5-9)

ACL, anterior cruciate ligament; IQR, interquartile range; MRI, magnetic resonance imaging; T0, baseline; T2, two-year follow-up.

Table 3. ACL feature changes over time

ACL Features	Improvement n (%)	Unchanged n (%)	Deterioration n (%)
Fiber continuity	30 (60)	18 (36)	2 (4)
Signal intensity	7 (14)	42 (84)	1 (2)
Slope	6 (12)	42 (84)	2 (4)
Distance of Blumensaat to ACL	9 (18)	41 (82)	0
Tension	2 (4)	46 (92)	2 (4)
Thickness of ACL	7 (14)	43 (86)	0
Clear boundaries	13 (26)	37 (74)	0
ACL tissue outside original insertions	14 (28)	34 (68)	2 (4)
Empty notch	22 (44)	28 (56)	0

ACL, anterior cruciate ligament.

ACL feature changes over time are presented in Table 3. Fiber continuity improved in 30 patients (60%), and the empty intercondylar notch resolved in 22 patients (44%). Improvement in other features ranged from 4% to 28%. Deterioration of ACL features was evidenced by fiber discontinuity (4%), signal intensity (2%), slope of the ACL with respect to the Blumensaat line (4%), ACL tension (4%) and deterioration of original insertions (4%). Most patients (76%) improved on a minimum of one feature (Table 4).

Improvements were noted for 16 patients (32%) on the Lachman test, for 1 patient (2%) on the KT-1000 arthrometer, and for 4 patients (8%) on the pivot shift test. Improvement on the Lachman test was caused by a change from soft to firm end points in 14 patients;

Table 4. Improvement of ACL features on MRI

Number of ACL features in which improvements were seen per individual patient n	Patients n (%)
0	12 (24)
1	14 (28)
2	5 (10)
3	6 (12)
4	5 (10)
5	4 (8)
6	2 (4)
8	2 (4)
9	0

ACL, anterior cruciate ligament; MRI, magnetic resonance imaging.

Table 5. Laxity changes

Laxity	n (%)
Lachman test	
Improvement	16 (32)
Decreased anterior translation	2 (4)
Change from soft to firm end point	14 (28)
Deterioration	6 (12)
Increased anterior translation	5 (10)
Increased anterior translation and change from firm to soft end point	1 (2)
Pivot shift test*	
Improvement	4 (8)
Deterioration	15 (30)
KT 1000 arthrometer†	
Improvement	1 (2)
Deterioration	5 (10)

*Missing n = 7: at baseline not applicable because of opposing muscle contraction.
†Missing data for one patient because of large leg circumference.

only 2 patients experienced decreased anterior translation. Six patients (12%) showed deterioration on the Lachman test, and 5 patients (10%) experienced an increase in anterior translation of at least 4 mm by KT-1000 arthrometer measurements. The mean maximal anterior translation, as measured by the KT-1000 arthrometer, increased from 11.3 (SD 2.1) mm at baseline to 12.1 (SD 2.9) mm at the 2-year follow-up (P = .009). Deterioration of the pivot shift test was present in 15 patients (30%) (Table 5).

The total score of ACL features at the 2-year follow-up was significantly associated with improvement on the Lachman test (odds ratio [OR], 0.8; 95% confidence interval [CI], 0.6 to 0.97; P = .029), i.e., the likelihood of improvement on the Lachman test is higher for a lower total score of the ACL features on MRI at 2-year follow-up. Analyzing the ACL features separately showed that improvement of the following ACL features was significantly associated with improvement on the Lachman test: signal intensity (OR, 7.3; 95% CI, 1.2 to 43.0; P = .012), clear boundaries (OR, 5.8; 95% CI, 1.5 to 22.7; P = .012), and assessment of the intercondylar notch (OR, 4.6; 95% CI, 1.3 to 16.5; P = .019). We found no relation between improvements on the following ACL features and Lachman test improvement: fiber continuity, slope of ACL with respect to the Blumensaat line, distance between the Blumensaat line and the ACL, tension, thickness, and assessment of original insertions. The number of improved ACL features was positively associated with improvement on the Lachman test (OR, 1.6; 95% CI. 1.1 to 2.2; P = .007); the likelihood of improvement on the Lachman test is higher when more ACL features were improved on MRI at 2 years. Because the percentages of improvement on the pivot shift test and KT-1000 arthrometer were low, we did not analyze their relation to improvement of ACL features.

DISCUSSION

Our study results suggest that MRI recovery from ACL rupture is possible in patients treated non-operatively. In particular, fiber continuity improved over time and the empty intercondylar notch resolved in almost half of the patients after 2 years. However, the other evaluated ACL features showed improvement in only some of the patients. The Lachman test result improved in one third of the patients, which means no translation anymore or ≥ 2+ decrease of anterior translation or a change from a soft to a firm end point. This clinical improvement showed a moderate negative relation with the total score of the ACL features at follow-up (the higher the total score the more abnormal features) and a moderate positive relation with the number of improved ACL features.

Our MRI recovery results are consistent with those found in previous studies.[13-18] To understand the ACL recovery process, it is important to understand what causes improvement in ACL features on MRI. Yoon et al.[28] showed that ACL morphologic features on MRI - as assessed by signal intensity, shape, and nonvisualization - correlates well with chronicity of the ACL rupture. In their study, ACL morphologic features, defined as "increased signal intensity and an edematous mass-like shape" dominated MRI findings until 3 months after rupture, whereas "low signal intensity and a band-like fragmented shape or nonvisualization" was most commonly present in MR images from patients with chronic (> 1 year) ACL ruptures. Their finding of "band-like fragmented shapes" in chronic ACL ruptures is consistent with our findings of ACL thickening and unclear boundaries.

Because our study follow-up was 2 years, all patients had chronic ACL rupture at the time of the second MRI. Observed improvements in fiber continuity and resolution of empty intercondylar notches might be related to scar tissue development. Tsai et al.[29] and Vahey et al.[30] showed in their studies that MRI is less accurate in diagnosing chronic ACL ruptures. A possible explanation for this low accuracy is the presence of scar tissue, which may complicate an adequate assessment. For knee stability, it is important to know whether the recovered fiber continuity, as demonstrated on MR images, is functional. Our results showed no relation between fiber continuity improvement and Lachman test improvement; this lack of association suggests that ACL fibers contributed nothing to stability. This hypothesis is supported by the high percentages of abnormal tension scores at follow-up. Our results suggest that ACL fibers showing recovery on MRI do not reflect improved laxity and support the findings of Chung et al.[13] and van Dyck et al.[18]. Our results showed that during follow-up of non-operatively treated patients, ACL physical examination should be the guidance in further treatment. Assessment of fiber continuity alone on MRI is inadequate. All ACL features

together should be taken into account, in particular signal intensity, clear boundaries, and assessment of the intercondylar notch.

We observed improvement on the Lachman test but deterioration over time when measuring the mean maximal anterior translation with the KT-1000 arthrometer. At first, these findings appear contradictory because both tests aim to measure anterior translation. However, additional analyses clarified this discrepancy. Lachman test improvement was caused primarily by a change from soft to firm end points (n = 14), and only 2 patients experienced decreased anterior translation. Change to a firm end point or decrease in anterior translation could result from remnant scar tissue attachment to the posterior cruciate ligament (PCL), the roof of the notch, or to the lateral femoral condyle.[31] This is also supported in the study of Dejour et al.[32] In this study, the ACL tear was classified as PCL healing when during arthroscopy the stump of the ACL was found to be healing on the PCL. The clinical evaluation of this group showed less laxity on the Lachman test and pivot shift test compared with the group with complete ACL tears. However, Dejour et al.[32] did not present results of the end point of the Lachman test.

Overall, we conclude that little functional recovery, based on laxity tests, occurred among our patients.

Diagnosis of a partial ACL rupture on MRI is difficult, as shown by van Dyck et al.[33] and Dejour et al.[32] Van Dyck et al.[33] found a low level of accuracy for diagnosing partial ACL tears on MRI compared with arthroscopic confirmation of partial ACL tears. For partial ACL tears, Dejour et al.[32] found no correlation between preoperative MRI findings and the arthroscopic type of ACL tear. However, Dejour et al.[32] showed that partial and complete tears could be distinguished with a combination of clinical examination and instrumented laxity testing with stress radiographs. In our study, we did not make a distinction between partial and complete ACL tears because only 2 patients of the 50 non-operatively treated patients in our study underwent arthroscopy.

Strengths of this study are its prospective design, use of an adequate sample size, and complete baseline and follow-up MRI and laxity tests for all patients. Furthermore, we analyzed changes in MRI scores and laxity tests to prospectively determine MRI and clinical recovery. Another strength is that we reported the individual ACL features on MRI. This study showed which features improved, which deteriorated, and which did not change over time. This information could be used in clinical practice.

Limitations

This study also has some limitations. Because all patients were treated non-operatively, we did not perform arthroscopic evaluation - the reference standard for diagnosing ACL rupture. Another limitation is that different MRI scanners and magnetic field strengths were used at baseline and follow-up. However, all MRI examinations included a set of routine clinical MRI pulse sequences of good diagnostic quality, and a recent study showed that the use of a 3.0 Tesla MRI scanner does not significantly improve diagnostic accuracy for ACL ruptures compared with a 1.5 Tesla MRI scanner.[34]

CONCLUSIONS

Two years after ACL rupture and non-operative management, patients experienced partial recovery on MRI and some knee laxity improvement. Improvement of ACL features on MRI correlates moderately with improved laxity.

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CHAPTER 5

Bone mineral density changes in the knee following anterior cruciate ligament rupture

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ABSTRACT

Objective: The pathophysiology of anterior cruciate ligament (ACL) rupture leading to knee osteoarthritis (OA) remains largely unknown. It seems that bone loss occurs after ACL rupture. The purpose of our study was to determine bone mineral density (BMD) changes in the knee after ACL rupture during 2-year follow-up period and to compare BMD changes between the injured and healthy contralateral knee.

Design: Patients were included in an observational prospective follow-up study within 6 months after ACL trauma and evaluated for 2 years. Patients were treated operatively or non-operatively. At baseline and at the one- and 2-year follow-ups, BMD was measured in six regions of the tibia and femur for both knees (medial, central, lateral) using a Dual-energy X-ray Absorptiometry (DXA) scanner.

Results: One hundred forty-one patients were included, with the following characteristics: 66% were male, median age at baseline was 25.3 (inter-quartile range 11.3) years, and 63% were treated operatively. After 1 year, BMD was significantly lower in all regions of the injured knee of the operatively treated patients compared to baseline. After 2 years, BMD was significantly increased, but remained lower than the baseline levels. In all regions for all measurements, the mean BMD was significantly lower in the injured knee than in the healthy contralateral knee.

Conclusions: During a 2-year follow-up period after ACL rupture, the BMD level in the injured knee was found to be lower than in the healthy contralateral knee. In operatively treated patients, the BMD decreased in the first year and increased in the second follow-up year.

INTRODUCTION

Anterior cruciate ligament (ACL) rupture is a common sports-related injury, with an annual incidence of approximately five per 10,000 persons in the general population.[1] Frobell et al. and a population based study of cruciate injuries in Sweden showed a higher incidence of approximately eight per 10,000 persons.[2,3] Osteoarthritis (OA) is a well-known long-term consequence of ACL rupture. A systematic review showed that highest rated studies regarding methodology, reported prevalences of 10-13% of knee OA 10 years after isolated ACL injury and they found prevalences of 21-48% for combined ACL injuries.[4] Better understanding of the pathophysiology of ACL rupture leading to OA may aid in preventing the onset or progression of OA and speed the development of disease-modifying OA drugs.

Previous studies suggest that changes in bone play a role in the development and progression of OA.[5-7] Bone metabolism increases in OA joints. Dieppe et al.[8] showed that, in patients with knee OA, a positive bone scintigraphy predicted loss of joint space. These findings suggest that the OA process is active in both cartilage and bone. Furthermore, biomarkers of cancellous bone collagen metabolism were found in high concentrations in osteoarthritic hips, suggesting increased bone turnover in the OA process.[9] Several animal studies showed a decrease in subchondral bone thickness after induction of OA, indicating that this is an early event in the OA process.[10-13] Hayami et al. observed subchondral bone loss soon after surgery in an OA-induced rat model, followed by an increase of the subchondral bone volume, resulting in subchondral bone sclerosis.[14] In early human OA, Bolbos et al. reported a reduction in bone volume, supporting the findings of the animal studies.[15] Clinical studies showed that degenerative changes were associated with an increase in BMD.[16-18] However, the patients in those studies had existing radiological and clinical OA. These findings suggest a biphasic process of BMD changes in OA: a reduction in BMD early on followed by an increase during more advanced phases.

To understand how post-traumatic OA develops, we are interested in the effect of ACL rupture on BMD early in the OA process. Indeed, other investigators have suggested that bone loss occurs in the aftermath of ACL rupture.[19,20] Ten studies investigating the influence of ACL injury and reconstruction on BMD of the involved lower extremity were included in a recent systematic review by Nyland et al.[19] All 10 studies reported that BMD or bone content did not return to normal levels after ACL injury or reconstruction. However, the studies measured BMD levels at different locations: patella, distal femur, proximal tibia, several hip sites, lumbar spine and calcaneus. Therefore, comparison of the studies is difficult. Another limitation is that the subgroup of studies that examined BMD in regions outside the knee evaluated only an indirect effect of ACL trauma on BMD, in terms of unloading. To evaluate both

direct (influence on the knee joint) and indirect effects on BMD, measurements in the distal femur and proximal tibia are necessary. Moreover, most of the included studies had small sample sizes: nine of the 10 studies included fewer than 50 patients. The range of time between ACL injury or reconstruction and BMD measurement varied between 4 months and 11 years. Due to this variation in follow-up time, it is difficult to distinguish between short- and long-term effects on BMD. Furthermore, identification of BMD changes over time was not possible because most of the studies had only one BMD measurement. A recent randomized controlled trial comparing BMD changes in the knee and hip of three different ACL reconstruction techniques found transient BMD loss in the knee in the first year post-operative.[21]

Owing to weaknesses and heterogeneity of the included studies in the previously mentioned systematic review[19] and the contradictory results compared with the ran-

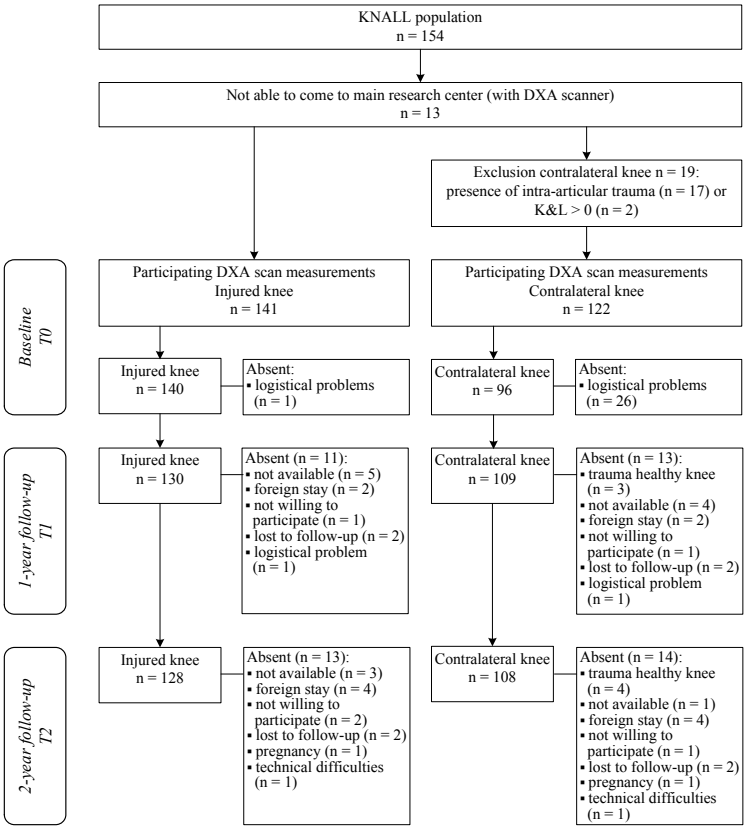

Figure 1. Overview of included patients.
Abbreviations; KNALL, KNee osteoArthritis anterior cruciate Ligament Lesion; DXA, Dual-energy X-ray Absorptiometry; K&L, Kellgren and Lawrence score.

domized controlled trial of Lui et al.[21], we aimed to investigate BMD changes in the knee following ACL rupture in a large prospective cohort by using standardized regions of interest (ROIs) in the knee. We used fixed time points: baseline, 1 year and 2 years. The purpose of our study was to determine BMD changes in the knee after ACL rupture during a 2-year follow-up period and to determine BMD changes between the injured and contralateral knee. Furthermore, we assessed the presence of interaction between BMD changes during follow-up and treatment choice and we assessed the relationship between activity level and BMD.

METHODS

Population

Between January 2009 and November 2010, 154 eligible patients were included in the KNee osteoArthritis anterior cruciate Ligament Lesion (KNALL) study. The patients were recruited from three hospitals in the Netherlands: Erasmus MC University Medical Center, Rotterdam; Medical Center Haaglanden, the Hague; and Reinier de Graaf Groep, Delft. The KNALL study is a prospective observational study of patients who visited the outpatient clinic within 6 months after trauma. Inclusion criteria were, age between 18 and 45 years, and presence of ACL rupture diagnosed by physical examination and magnetic resonance imaging (MRI). Patients who did not speak the Dutch language; those with previous ACL injury or meniscus or cartilage damage; those with previous surgery of the involved knee; those with disabling co-morbidity; and those already with osteoarthritic changes on X-ray (Kellgren and Lawrence [K&L] grade > 0) were excluded. The contralateral knee of each included patient comprised a control group. The included patients were evaluated at baseline, and after 1 and 2 years. BMD measurements were made in 141 of 154 of the included patients. The 13 patients without BMD measurements were not willing to visit the main research center to have Dual-energy X-ray Absorptiometry (DXA) scans performed. Contralateral knees with radiographic knee OA (K&L score > 0) or ACL injury or meniscus or cartilage injury were excluded. One hundred twenty-two contralateral knees were included in the control group; 19 were excluded because of intra-articular knee injury (n = 17) or presence of radiographic OA (n = 2) at baseline. One patient was not available at baseline for DXA scan measurement, but at follow-up he participated in both DXA scan measurements. Of the finally 122 contralateral knees of the included patients, 96 were measured at baseline, 109 at the 1-year follow-up and 108 at 2-year follow-up (see Fig. 1).

The decision for operative or non-operative treatment was made by the patient and orthopaedic surgeon. In the operatively treated patients the following fixation methods were used. By using hamstring tendon (HT) grafts or combination of HT and allografts,

on the femoral side the tendon was fixed with an extracortical button technique (Endobutton; Smith & Nephew) or with a Bio-TransFix implant (Arthrex) and on the tibial side with a resorbable interference screw (Smith & Nephew) or a Delta Tapered Bio-Interference Screw (Arthrex) was used for the fixation and if the torque was below 15 N, then a staple (Arthrex) was placed as extra fixation. By using bone-patella tendon-bone grafts, both sides were fixed with a resorbable interference screw (BioRCI; Smith & Nephew).

DXA scan measurement

The knee BMD was measured by DXA using a Lunar Prodigy scanner (GE Lunar Corp., Madison, WI, USA). Because the standard program of the DXA scanner had no knee protocol, we chose to use the spine protocol, which fit our purpose best in terms of predefined field of view.

The position of the patient was standardized. The lower extremity was fixed in a plastic device and the knee slightly flexed (10°). The leg was fixed in a 15° internal rotation for positioning the patella centrally. The positioning laser light was used to position the center of the scanner arm 8 cm below the tuberositas tibiae. This resulted in antero-posterior views.

We outlined the contours of the femur and tibia by placing anatomical landmark points using the freely available active shape model toolkit software package (Manchester University, Manchester, UK). Each landmark point was placed on corresponding positions on each scan. Using specific anatomical landmark points, we automatically extracted six ROIs: medial, central, lateral in the tibia, and medial, central and lateral in the femur (see Fig. 2 for regions and used landmark points). The height and placement of the regions were based on reference lines between landmark points that indicated the medial and lateral sides of the tibia and femur (see Fig. 2). In the tibia, the regions run from the lower point of these lines up to a point 30% beneath the top of the line. This was to assure that the regions were positioned below the subchondral bone. In the femur, the bottom of the regions was positioned 10% of the length of the reference line above the lowest point, while the top was placed at 50%. The regions in the femur were positioned such that the medial and lateral ROIs were placed inside the respective condyles. The most lateral and medial border of the ROIs in the tibia and femur were positioned parallel to the outline of the tibia and femur, at a distance from the outline of 5% of the width of the bone. The area without bone in the central region of the femur, which interfered with the femoral notch, was excluded from BMD analysis (Fig. 2).

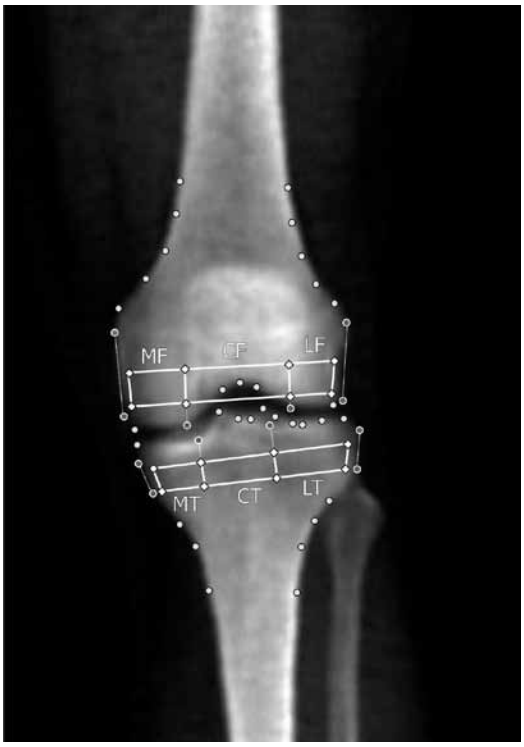

Figure 2. Determination of 6 regions of interest (ROIs) by using landmark points. MT, medial tibia; CT, central tibia; LT, lateral tibia; MF, medial femur; CF, central femur; LF, lateral femur.

Reproducibility

The test-retest consisted of two aspects. First, the test-retest for placing landmark points was assessed in 25 scans, which were randomly chosen, by placing the landmark points twice. The time between the first and second placement of the landmark points was 1 month. Second, the test-retest for positioning the patients under the DXA scanner was assessed during the 2-year follow-up in 50 patients by measuring the patients at the beginning and end of their visit. After the first scan the patients got up from the scanner bed, then we did the other measurements (physical examination and questionnaires) and at the end of the visit the patient lied down again on the scanner bed, resulting in repositioning of the patient.

Questionnaire

At all visits the patients were asked to fill in the Tegner activity score.[22] At baseline the patients were asked to fill in their activity level pre-injury and their activity level at the moment of their baseline measurements. The Tegner activity score is a knee related activity scale where work and sport activities are graded. Score 10 represents

competitive sports as soccer (national and international elite) and score zero represents sick leave or disability pension because of knee problems.

Statistical analysis

Statistical analyses were performed with IBM SPSS Statistics 20.0 (SPSS Science Inc., Chicago, USA).

The reproducibility of the DXA scan measurements was assessed by determining the intraclass correlation coefficient (ICC; two-way random effects model, absolute agreement).

Generalized estimating equation (GEE) analyses were conducted to analyze if the BMD levels were different depending on the time of measurement (T0, T1 and T2), side (injured and contralateral knee) and treatment choice (non-operative and operative treatment). The GEE model takes into account the correlation between left and right knees within one person and the correlation between the time points within one person. We adjusted for age, gender and body mass index (BMI). We tested the assumption that the residuals of all BMD analyses had a normal distribution.

We used linear regression analyses to explore if the BMD values at baseline were associated with the time between trauma and DXA scan measurement at baseline. We hypothesized that the BMD values at baseline of the patients can be influenced by a difference in pre-trauma activity level. Thereby we hypothesized that the pre-trauma activity level of operatively treated patients would be higher than the non-operatively treated patients. We used the Mann-Whitney *U* test to explore whether the pre-trauma Tegner activity score differed between the operatively and non-operatively treated patients.

Significance was assumed for a P value <0.05. We took into account the effects of multiple testing both within ROIs and between ROIs. Within ROIs we have used the bonferroni adjustment in the *post-hoc* analysis of the GEE models. Between ROIs we adjusted the significance threshold to 0.008 (α level/k tests: 0.05/6 ROIs = 0.008).

RESULTS

The characteristics of the included patients are presented in Table 1. The time between injury and baseline DXA scan measurement had no influence on the BMD levels in all ROIs. Consequently, we decided not to correct for the variable time between injury and baseline visit.

Table 1. Patient characteristics

	n = 141
Baseline characteristics	
Age (years)	25.3 (11.3)
Gender (female) - *n (%)*	48 (34)
BMI (kg/m^2)	23.7 (4.3)
Injured side (right) - *n (%)*	75 (53)
Time, injury to DXA measurement at baseline (months)	2.6 (2.3)
Treatment variables during follow-up	
Treatment - *n (%)*	
Non-operative	47 (33)
Operative	90 (64)
Lost to follow-up	4 (3)
Time, injury to reconstruction (months)	5.7 (5.1)
Graft type - *n (%)*	
HT	82 (91)
BPTB	5 (6)
Combination (HT/allograft)	3 (3)
Activity	
Tegner score pre trauma	
All patients	9 (2)
Non-operative	8 (3)*
Operative	9 (2)
Tegner score at baseline	
All patients	3 (2)
Non-operative	3 (2)
Operative	3 (1)
Tegner score at 1-year follow-up	
All patients	6 (3)
Non-operative	6 (3)
Operative	6 (4)
Tegner score at 2-year follow-up	
All patients	7 (4)
Non-operative	5 (3)*
Operative	7 (4)

Data are presented as median (interquartile range), unless otherwise indicated.
*Significant difference (*P* value < 0.05) between non-operatively and operatively treated groups.
Abbreviations: BPTB, bone – patellar tendon – bone; HT, hamstring tendon.

Reproducibility

The ICCs of the BMD levels in the ROIs for placing landmark points ranged from 0.89 to 1.00. For positioning of the patient under the DXA scanner, the ICCs of the BMD levels in the ROIs ranged from 0.85 to 0.96 in the injured knee and from 0.88 to 0.97 in the contralateral knee.

Table 2. Bone mineral density levels in injured and contralateral knees

ROI	T0 Injured n = 140 Contralat n = 96 Mean (SD)	T1 Injured n = 130 Contralat n = 109 Mean (SD)	T2 Injured n = 128 Contralat n = 108 Mean (SD)	T0-T1 *P* value	T1-T2 *P* value	T0-T2 *P* value
MT injured	0.95 (0.13)	0.92 (0.13)	0.95 (0.14)	**< 0.001**	**<0.001**	1.000
contralat	0.99 (0.12)	0.98 (0.12)	0.99 (0.12)	**0.016**	0.086	1.000
CT injured	0.96 (0.15)	0.90 (0.15)	0.92 (0.16)	**< 0.001**	**0.001**	**< 0.001**
contralat	1.01 (0.15)	0.99 (0.15)	0.98 (0.16)	**0.001**	0.205	**< 0.001**
LT injured	0.96 (0.1422)	0.91 (0.14)	0.94 (0.15)	**< 0.001**	**< 0.001**	**0.047**
contralat	1.01 (0.14)	0.99 (0.14)	0.99 (0.14)	**< 0.001**	1.000	**0.002**
MF injured	1.07 (0.12)	1.00 (0.13)	1.03 (0.13)	**< 0.001**	0.718	**< 0.001**
contralat	1.11 (0.12)	1.11 (0.12)	1.10 (0.11)	1.000	1.000	0.539
CF injured	1.36 (0.15)	1.32 (0.15)	1.36 (0.16)	**< 0.001**	**< 0.001**	1.000
contralat	1.39 (0.13)	1.41 (0.14)	1.42 (0.13)	**0.038**	0.559	**< 0.001**
LF injured	1.24 (0.21)	1.19 (0.21)	1.25 (0.22)	**0.001**	**< 0.001**	1.000
contralat	1.28 (0.19)	1.28 (0.20)	1.30 (0.21)	1.000	0.141	0.309

Abbreviations: contralat, contralateral; MT, medial tibia; CT, central tibia; LT, lateral tibia; MF, medial femur, CF, central femur; LF, lateral femur; SD, standard deviation.
Bone mineral density is presented in g/cm^2. All analyses were adjusted for age at baseline, BMI and gender. In bold, *P* values < 0.05.

BMD changes during follow-up

The BMD of the injured knee was significantly lower at the 1-year follow-up in all ROIs, compared to baseline. At the 2-year follow-up, BMD was significantly increased again compared to the 1-year follow-up, in all ROIs except for the medial tibia (MT). The BMD levels in the central (CT) and lateral tibia (LT) and medial femur (MF) remained significantly lower than at baseline. In the contralateral knee, BMD changes were much smaller. In the tibia, all regions showed a slight but significant decrease in the first follow-up year, which did not recover by the 2-year follow-up. In contrast, BMD in the femur did not change or even increased slightly, which was significant after 1 and 2 years in the central region of the femur (Table 2).

BMD differences between injured and contralateral knees

In all ROIs at all time points the BMD level of the injured knee was significantly lower than the BMD level of the contralateral knee (Table 3).

Table 3. Bone mineral density difference between injured and contralateral knee at all time points

	T0		T1		T2	
ROI	Delta BMD (contralateral-injured) Mean (SD)	*P* value	Delta BMD (contralateral-injured) Mean (SD)	*P* value	Delta BMD (contralateral-injured) Mean (SD)	*P* value
MT	0.04 (0.07)	< **0.001**	0.06 (0.07)	< **0.001**	0.04 (0.07)	< **0.001**
CT	0.05 (0.07)	< **0.001**	0.09 (0.07)	< **0.001**	0.06 (0.06)	< **0.001**
LT	0.05 (0.07)	< **0.001**	0.08 (0.08)	< **0.001**	0.05 (0.07)	< **0.001**
MF	0.03 (0.09)	**0.001**	0.08 (0.10)	< **0.001**	0.07 (0.09)	< **0.001**
CF	0.03 (0.10)	0.008	0.09 (0.10)	< **0.001**	0.06 (0.10)	< **0.001**
LF	0.05 (0.15)	**0.001**	0.10 (0.16)	< **0.001**	0.07 (0.16)	< **0.001**

Abbreviations: MT, medial tibia; CT, central tibia; LT, lateral tibia; MF, medial femur, CF, central femur; LF, lateral femur; SD, standard deviation.
Delta bone mineral density is presented in g/cm². In bold, *P* values < 0.008 (adjusted for multiple testing).

Influence of treatment on BMD

Forty-seven patients (33%) were treated non-operatively, 90 patients (64%) operatively, and the treatment given to four patients was unknown because of the following reasons: lost to follow-up (n = 2), foreign stay during both follow-up years (n = 1), and not willing to participate (n = 1). The operatively treated group had significantly higher Tegner activity scores both pre-trauma and at the 2-year follow-up compared to the non-operatively treated group (Table 1).

The BMD levels of the operatively treated group showed the same pattern during follow-up as was observed for the whole group. In the non-operatively treated group, the BMD levels did not significantly change during follow-up, except for the central region of the tibia. In this region, the BMD level had decreased significantly in the first year and decreased even further in the second follow-up year. At baseline, the operatively treated patients had a higher BMD than the non-operatively treated patients. After 1 year, all regions of the tibia and femur had lower BMDs in the operative group than in the non-operative group, except for the lateral femur (LF). At 2 years' follow-up, the BMDs in all regions, except the medial and central region of the femur, were higher again in the operative group than in the non-operative group. However, all these differences did not reach significance (Table 4).

In the non-operatively treated group, the injured knee had a significantly (*P* value <0.008) lower BMD level than the contralateral knee at all time points in all ROIs of the

Table 4. Bone mineral density of injured knees in non-operatively and operatively treated patients

ROI*	T0 Non-operative n = 47 Operative n = 89 Mean (SD)	T1 Non-operative n = 45 Operative n = 85 Mean (SD)	T2 Non-operative n = 46 Operative n = 82 Mean (SD)	T0-T1 P value	T1-T2 P value	T0-T2 P value
MT non-operative	0.94 (0.14)	0.94 (0.13)	0.94 (0.15)	0.629	0.430	1.000
operative	0.96 (0.12)	0.91 (0.13)	0.96 (0.13)	**< 0.001**	**< 0.001**	1.000
CT non-operative	0.93 (0.17)	0.91 (0.17)	0.90 (0.18)	**0.006**	1.000	**0.003**
operative	0.97 (0.14)	0.90 (0.13)	0.94 (0.15)	**< 0.001**	**< 0.001**	**0.002**
LT non-operative	0.93 (0.14)	0.92 (0.15)	0.92 (0.15)	0.138	0.950	0.675
operative	0.98 (0.14)	0.90 (0.13)	0.96 (0.15)	**< 0.001**	**< 0.001**	0.098
MF non-operative	1.05 (0.14)	1.05 (0.13)	1.03 (0.14)	0.978	1.000	0.299
operative	1.08 (0.11)	1.01 (0.13)	1.03 (0.12)	**< 0.001**	0.175	**< 0.001**
CF non-operative	1.34 (0.14)	1.35 (0.17)	1.36 (0.18)	1.000	1.000	0.902
operative	1.37 (0.15)	1.31 (0.15)	1.36 (0.15)	**< 0.001**	**< 0.001**	0.931
LF non-operative	1.18 (0.21)	1.18 (0.23)	1.21 (0.22)	1.000	0.086	0.440
operative	1.27 (0.21)	1.19 (0.21)	1.27 (0.23)	**< 0.001**	**< 0.001**	1.000

Abbreviations: MT, medial tibia; CT, central tibia; LT, lateral tibia; MF, medial femur, CF, central femur; LF, lateral femur; SD, standard deviation.

BMD is presented in g/cm². All analyses were adjusted for age at baseline, BMI and gender. In bold, *P* values < 0.05.

*Bone mineral density differences between non-operatively and operatively treated patients in all ROIs and at all time points are not significant.

tibia and femur, except for the central and lateral region of the femur. In the operatively treated group, all ROIs in the tibia of the injured knee had significantly (*P* value <0.008) lower BMDs than the contralateral knee at all time points. For the femoral regions similar findings were found. Only at baseline these differences were not significant.

Influence of activity on BMD

We found a significant positive relationship between the Tegner activity score and the BMD levels at 1- and 2-year follow-up in the injured knee in all ROIs (beta ranged from 0.018 to 0.024; *P* value <0.008; and 0.018 to 0.033; *P* value <0.008 respectively). At the 2-years follow-up we also found a significant positive relationship between the Tegner activity score and the contralateral BMD levels of all tibia regions and the MF region (beta ranged from 0.016 to 0.023; *P* value <0.008).

DISCUSSION

We found in patients with a recent ACL rupture that operatively treated patients experienced a decrease in BMD in all ROIs in the femur and tibia in the first year after ACL rupture, followed by an increase in the second follow-up year. BMD levels in the non-operatively treated patients were unchanged from baseline at both follow-ups. For all measurements, the BMD of the injured knee was lower than that of the contralateral knee in all ROIs, in both the operatively and non-operatively treated patients.

The findings of our study are in accordance with the results of most previous studies.[19,21] It is well-known that BMD loss is related to a reduction in either load or physical activity.[23] After an ACL injury and after reconstruction there will be a period of reduced weight bearing and disuse. We can partially clarify the findings of the BMD decrease in the first year in the injured knee of the operatively treated patients. Exploratory analysis (not presented) showed a significant negative relationship between delta BMD levels (baseline - follow-up 1) and the time between reconstruction and DXA measurement at follow-up 1. Thus, the reduction in BMD at follow-up 1was not as severe in patients for whom the time between reconstruction and DXA measurement was greatest. Presumably, these patients were already more active at follow-up 1. Nine patients were reconstructed after follow-up 1. These patients also experienced a BMD decrease in the first year, but after knee reconstruction in the second follow-up year, the BMD decreased further. In these nine patients, the decrease in BMD in the first year could be trauma-related and in the second year reconstruction-related. In both circumstances, a drop in physical activity is expected. These findings suggest that inactivity after trauma and after reconstruction can influence BMD. The positive relationship between the Tegner activity score and BMD levels at the first and second follow-ups in the injured knee supports this explanation. However, isolated rupture of the medial collateral ligament seemed to have no long-term effect on BMD, although the immobilization period after trauma was the same as in patients with an ACL injury.[24] This suggests that a period of decreased weight bearing and disuse after ACL trauma or reconstruction is not the only factor that influences BMD. A possible explanation might be that the load on the injured knee after ACL trauma is changed permanently. This could also clarify the observed difference in BMD between the injured and contralateral knees at all time points in all patients in our study. Unfortunately, we had no information concerning the loads on the two knees separately.

A key question remains: Is long-term disuse of the injured knee the only factor that influences BMD in the knee? It is possible that other trauma-related factors, such as a direct effect of the trauma, are involved. First, BMD changes in the operatively treated

patients might be tunnel-related. However, all ROIs located in- and outside the drilled tunnel had the same pattern regarding BMD changes. Another possible explanation for the decrease in BMD is the presence of bone marrow lesions, which are common after an ACL trauma.[25,26] Frequently, a characteristic pattern of bone marrow lesion occurs after an ACL rupture, located in the lateral femur condyle and the postero-lateral tibia plateau.[25] Counterarguments are, firstly, that bone marrow lesions after an ACL rupture are often not present in all regions of the tibia and femur, whereas in our study, the pattern of BMD changes was the same in all ROIs. Secondly, it has been shown that, 1 year after ACL trauma, the number and volume of bone marrow lesions are reduced.[27,28] Assuming that the bone marrow lesions were reduced after 1 and 2 years in our study, the BMD level in the injured knee was still lower than in the contralateral knee after 1 and 2 years. To our knowledge, no studies have investigated the relationship between bone marrow lesions after an ACL rupture and BMD changes in these areas. However, OA-related bone marrow lesions seem to have a relationship with BMD changes.[29,30] A third explanation for the BMD decrease might be the influence of local biochemical processes induced after ACL rupture. These inflammation-related factors may affect cartilage and bone and may play a role in the initiation of the OA process.[31,32] Finally, the difference observed between the operatively and non-operatively treated patients could be explained by the fact that reconstruction of the ACL is a second trauma, with new bone marrow lesions arising due to the drilled tunnel and the release of inflammatory factors.

It is noteworthy that at baseline measurements, 2.6 months after trauma, already a difference in BMD was present between the injured and contralateral knees. This may be caused by inactivity and/or the previously mentioned trauma-related factors.

With the test-retest we demonstrated that our measurements, positioning of the patient, and placing of the anatomical landmark points, had good to excellent reproducibility. Additional strengths of our study are its large sample size and prospective study cohort design. Most previous studies[19,20] which investigated the influence of an ACL rupture on the BMD enrolled fewer than 50 patients. To measure both the direct effect and the unloading effect of ACL trauma and reconstruction on BMD, we measured BMD in the knee: 3 ROIs in the proximal tibia and 3 ROIs in the distal femur. Studies that measure BMD levels outside the knee can evaluate only the effect of unloading. In selecting the ROIs, we chose locations in cancellous bone. This region is more homogeneous in terms of bone structure than the area just below the articular cartilage, where the subchondral bone plate causes more variation due to sclerosis[33], which in turn can influence BMD levels. Additionally, we analyzed subchondral regions in the tibia (data not presented) and found the same BMD pattern as for the regions described and used for this study.

This study had also some limitations. We could not investigate the previous findings of a decrease in BMD in the patella[19], because we had no lateral view of the DXA scans. Another limitation is that our findings cannot be directly linked to OA, because a longer follow-up time is necessary.

Future research should investigate the relationship between the BMD changes that occur after ACL rupture and the development of degenerative features. Moreover, it is important to know if the BMD in this population will normalize or increase in the future, because the findings in animal and clinical studies suggest a biphasic process of BMD changes in OA.[10-13,15-18] In a separate study, we found in a group of 30 non-operatively treated patients that BMD in the injured knee was lower than in the contralateral knee 5 years after ACL rupture, but this difference did not reach significance (unpublished data). Thus, long-term follow-up of that patient class in this new prospective cohort is important.

In conclusion, the results of this study show that BMD in the knee decreased after ACL trauma and reconstruction, and after 2 years reached nearly baseline (post-traumatic) levels but remained lower than the contralateral knee. We could partially explain these changes in BMD by the physical inactivity that followed the ACL rupture and reconstruction. The observed BMD differences at all measurements between injured and contralateral knees might be a result of differences in load or a direct effect of the trauma on BMD in the knee.

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CHAPTER 6

Degenerative changes on MRI five years after non-operatively treated anterior cruciate ligament rupture

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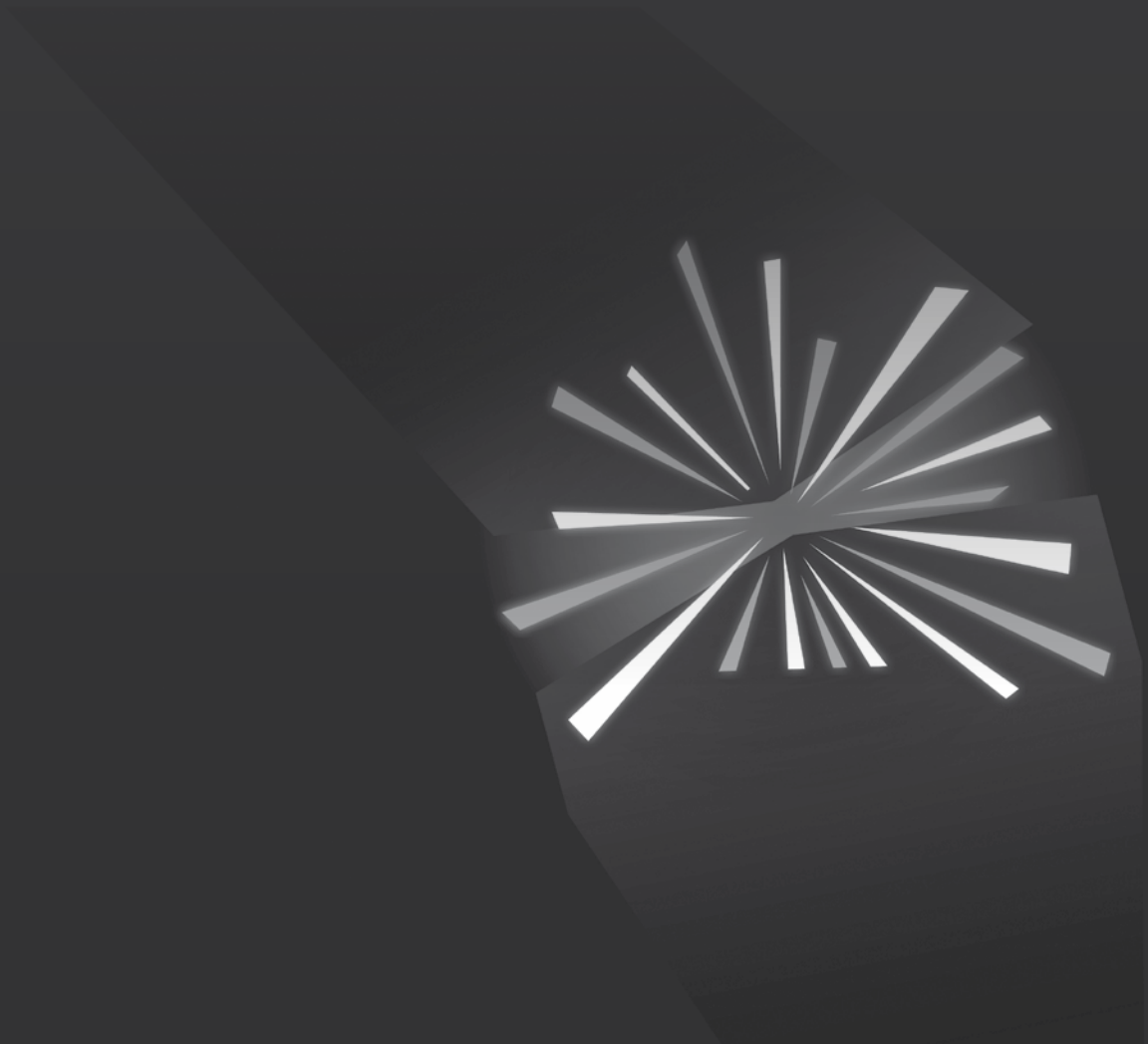

ABSTRACT

Background: MRI has become an important tool for OA research because of its capability to visualize all structures in the knee joint.
Aim: To determine which OA features are detectable in ACL-deficient knees, assessed by MRI Osteoarthritis Knee Score (MOAKS), and how these features progress during a 5-year follow-up.
Patients and methods: Patients who had a complete ACL rupture 5 years prior, confirmed by physical examination and MRI within 6 months of trauma, were eligible for inclusion. Inclusion criteria were no surgical intervention for both knees to date, age at trauma ≤ 45 years, and no clinical signs of OA at the time of trauma. All MRI scans were evaluated according to MOAKS.
Results: Thirty patients were included. Mean age at trauma was 34.0 (standard deviation 6.8) years. At follow-up, 7 patients showed progression of cartilage defects in the patello-femoral compartment, 5 in the medial tibio-femoral compartment, and 4 in the lateral tibio-femoral compartment. Four patients had progression of osteophytes in the patello-femoral compartment, 8 in the medial tibio-femoral compartment, and 3 in the lateral tibio-femoral compartment. Medial meniscus pathology progression was scored in 6 patients, and of the lateral meniscus in 7 patients. At follow-up, 2 patients (6.7%) met the MRI-based definition of patello-femoral OA and 7 patients (23.3%) of tibio-femoral OA.
Conclusions: MOAKS can detect degenerative changes in chronic ACL-deficient patients. Progression of cartilage, osteophytes, or meniscus pathology, as assessed with MOAKS, occurred in 70% of patients who were treated non-operatively 5 years after ACL rupture.

INTRODUCTION

Osteoarthritis (OA) is a well-known, long-term consequence of anterior cruciate ligament (ACL) rupture. Previous studies have reported OA prevalences of 10% to 90% at 10 to 20 years after ACL injury.[1,2] How ACL rupture leads to radiologic knee OA remains largely unknown, but it has been suggested that joint damage associated with ACL injury plays a role in initiating OA.[3]

In clinical practice, conventional radiography is the most common imaging modality to diagnose and monitor knee OA over time. A disadvantage of radiography for OA research is its lack of sensitivity in identifying early degenerative features, because it can only detect bony changes and joint space narrowing, which are indirect measures of cartilage thickness and meniscus integrity.[4] OA is generally regarded as a disease of the whole joint with involvement of all tissues.[5,6] Hence, magnetic resonance imaging (MRI) has become an important tool for OA research because of its capability to visualize all structures in the knee joint.[4,7]

Two types of MRI scoring methods for assessing knee OA features can be distinguished: quantitative and semi-quantitative. Semi-quantitative methods allow the multi-tissue assessment of OA features in the knee with use of conventional MRI methods. However, semi-quantitative methods are more observer-dependent than quantitative methods. Both techniques have shown to be reliable and sensitive for detecting structural changes on MRI.[8]

Several semi-quantitative MRI scoring systems exist for knee OA: the Whole-organ Magnetic Resonance Imaging Score (WORMS)[9], Knee Osteoarthritis Scoring System (KOSS)[10], and Boston Leeds Osteoarthritis Knee Score (BLOKS)[11]. Recently, the MRI Osteoarthritis Knee Score (MOAKS)[12] was developed based on the limitations and merits of WORMS and BLOKS, and its reliability was assessed in the Progression Subcohort of the OA Initiative (OAI).[12] To date, no other studies using MOAKS have been published. More data are necessary for evaluating the validity and responsiveness of MOAKS in different OA stages.

The aim of this study was to assess which OA features are detectable in ACL-deficient knees, as assessed by MOAKS, and how these OA features progress during a 5-year follow-up. Secondly, we determined the percentage of patients who met a previously published MRI-based definition for knee OA.[13]

METHODS

Population

Patients who consulted an orthopedic surgeon in one of the participating centers between 1 November 2004 and 30 July 2007 because of a complete ACL rupture, confirmed by physical examination and MRI within 6 months after trauma, were eligible for inclusion. Eligible patients were identified from databases of the following two participating hospitals in the Netherlands: Erasmus MC University Medical Center Rotterdam and Medical Center Haaglanden, The Hague. Data from four MRI Centers (Rotterdam, Amsterdam, Den Bosch, and Groningen) were also used. Patients, who had visited these centers between 1 January 2006 and 31 December 2007 for MRI of the knee because of suspected ACL rupture, were contacted. Inclusion criteria were: no prior surgical intervention for both knees, age at trauma ≤ 45 years, no history of OA-related symptoms or clinical signs at the time of trauma, and initial MRI at a magnetic field strength of ≥ 0.5 Tesla. Patients who did not speak Dutch or those with previous intra-articular knee trauma or arthroscopy of the injured or contralateral knee during the follow-up period were excluded. All eligible patients were invited by letter to visit the outpatient clinic of one of the two participating orthopedic surgery departments. Written informed consent was obtained from all included patients and the study was approved by the institutions' Medical Ethics Committees.

Measurements

All included patients completed the following questionnaires: Knee injury and Osteoarthritis Outcome Score (KOOS)[14,15], Tegner score[16], International Knee Documentation Committee (IKDC) Subjective knee score[15,17], and Patient Rated Improvement regarding knee stability.

At baseline, the MRI scans were acquired on different MRI scanners with magnetic field strengths of 0.5 (n=5), 1.0 (n=9) and 1.5 (n=16) Tesla. At follow-up, all MRI scans were acquired on the same type of MRI scanner at 1.5 Tesla. The patients' legs were positioned neutrally. All MRI examinations included the following MRI pulse sequences: sagittal and coronal proton density weighted turbo spin echo (TSE) sequence (slice thickness 3 mm, TR/TE: 2700/27 ms), coronal T2-weighted TSE sequence with fat saturation (slice thickness 3 mm, TR/TE: 5030/71 ms), axial proton density and T2-weighted TSE sequence (slice thickness 3 mm, TR/TE: 3500/25/74 ms) and sagittal 3D water excitation double-echo steady state sequence (slice thickness 1.5 mm, TR/TE 21.35/7.97 ms).

All MRI scans were evaluated by a researcher (BvM), who is also a physician, blinded for clinical information. Baseline and follow-up MRI scans were assessed

concurrently and the order of MRI measurements was known. At follow-up, MRI was also performed on the contralateral knees to serve as controls.

OA features on MRI

All MRI scans (injured knee at baseline, both knees at follow-up) were evaluated with the semi-quantitative MOAKS scoring system.[12] MOAKS assesses structures and features potentially relevant in knee OA (categorized from 0 to 3 or scored as absent/ present): subchondral bone marrow lesions (BMLs) and cysts, articular cartilage morphology, osteophytes, menisci (morphology, signal intensity and extrusion), anterior and posterior cruciate ligaments, synovitis, joint effusion, intra-articular loose bodies, and periarticular ligaments and cysts/ bursitis. In MOAKS, the patella, femur, and tibia are divided into 14 articular sub-regions. For our data analysis, we combined subregions and defined 3 compartments for assessing BMLs, cartilage and osteophytes: patello-femoral (medial and lateral patella, medial and lateral femoral trochlea), medial tibio-femoral (medial central and posterior femur, anterior, central and posterior medial tibia), lateral tibio-femoral (central and posterior lateral femur, anterior, central and posterior lateral tibia). The medial and lateral meniscus abnormalities were scored in 3 subregions: anterior horn, body, and posterior horn.

To ensure proficiency in implementation of MOAKS, our reader (BvM) underwent an extensive training program together with other readers of our research team. First, we studied the MOAKS description by Hunter et al.[12], discussed this description among our team and obtained additional information from the authors on the scoring of certain features. Second, we organized 4 training sessions of 2 hours each during which all MOAKS features were thoroughly reviewed using several MRI examples, under the supervision of an experienced musculoskeletal radiologist (EO, with 10 years of experience in musculoskeletal MRI in clinical and research settings). Additionally, after each session, several knee MRIs were scored by all trainees, which were evaluated at the next session. Finally, all trainees scored a test set of 20 MRIs of different OA cohorts at our institution. Afterwards, a consensus meeting was held to determine the correct interpretation of all scores of these MRIs.

To assess the reliability in the present study, BvM and EO independently read MRIs of 15 knees.

Definition of progression of OA features on MRI

We composed the following definitions of progression of the MOAKS features.

Cartilage
Progression of a cartilage defect was determined based on changes in the cartilage defect size and/ or% full-thickness loss at follow-up compared to baseline. The following principles were leading for the overall definition:
- if% full-thickness loss had increased, this was defined as progression, regardless of changes in size of the affected area;
- if% full-thickness loss had decreased, this indicated improvement, irrespective of changes in size of the affected area;
- if% full-thickness loss had remained unchanged, the change of the overall definition was equal to the change in size of the affected area.

Osteophytes
Progression was defined as a change of osteophyte grade from 0 or 1 at baseline to grade 2 or 3 at follow-up or from grade 2 to 3. Changes from grade 0 to 1 or grade 1 to 0 were defined as no change.

Meniscus
Progression of meniscal pathology was defined as incidence of meniscal hypertrophy, meniscal cyst, maceration or tear regardless of other changes in these items. The incidence of meniscal signal was considered progression if the other items did not improve. The following definition of improvement was defined: a) decrease of meniscal hypertrophy if there was no incidence of cyst, maceration and tear; b) disappearance of a tear at follow-up if there was no incidence of hypertrophy, cyst and maceration; c) disappearance of meniscal signal at follow-up, if there was no incidence of hypertrophy, cyst, maceration, and tear.

We did not define progression of BMLs because, at baseline, the BMLs were likely trauma-related bone bruises and, if they were not, it was difficult to distinguish trauma-related from degenerative BMLs.

OA definition on MRI

For the assessment of presence of OA in our population, we used the definition by Hunter et al.[13] that proposes the following definition of patello-femoral OA: presence of a definite osteophyte and partial or full-thickness cartilage loss involving the patella and/or anterior femur. Tibio-femoral OA was defined as: presence of both group A features (definite osteophyte formation and full-thickness cartilage loss) or one group A feature and two or more group B features (subchondral bone marrow lesions or cysts not associated with meniscal or ligamentous attachments, meniscal subluxation, maceration or degenerative (horizontal) tear, partial thickness cartilage loss (where

full-thickness loss is not present) and bone attrition). For determining the percentage OA in our study, based on the above described MRI definition, we asked the authors for additional information. The following conventions were used: the cut-off point for "definite osteophyte" was grade 2 on MOAKS; "partial meniscus maceration" was also a positive group B feature; meniscus extrusion graded 1 or more on MOAKS was scored as a positive group B feature. As bone attrition is not scored by MOAKS, we did not include this feature for determining the presence of OA.

Statistical analysis

All statistical analyses were performed with IBM SPSS Statistics for Windows (Version 20.0., IBM Corp., Armonk, NY). Descriptive statistics were used for analyses of the baseline characteristics and degenerative features assessed on MRI. Mean and standard deviation (SD) were presented for the variables that were normally distributed. Median and inter-quartile range (IQR) were presented for the non-normally distributed variables.

For the assessment of the inter-rater reliability, we determined the Prevalence – Adjusted Bias-Adjusted Kappa (PABAK), which takes into account both the prevalence of a positive finding and bias of each observer for reporting a positive finding.[18]

RESULTS

In total, we included 30 patients from 2 hospitals and 4 MRI centers. Figure 1 shows the flow chart of inclusion of eligible patients. Patient characteristics are presented in Table 1.

Table 1. Patient characteristics (n = 30)

Age at trauma in years – *mean (SD)*	34.0 (6.8)
Gender (female) – *n (%)*	9 (30)
Body mass index, kg/m²	25.0 (6.7)
Time from trauma to follow-up MRI in months – *mean (SD)*	59.9 (± 5.7)
Tegner activity scale pre-trauma	7 (2)
Tegner activity scale at follow-up	6 (3)
KOOS at follow-up	
Pain	88.9 (18.1)
Symptoms	91.1 (14.3)
ADL	97.1 (16.9)
Sport	77.5 (45.0)
QOL	62.5 (25.0)

Table 1. Patient characteristics (n = 30) (continued)

IKDC subjective at follow-up	81.0 (26.7)
Patient-rated improvement (knee stability) – *n (%)*	
improvement	16 (53)
unchanged	9 (30)
deterioration	5 (17)

Data are presented as median (interquartile range), unless otherwise indicated.
Abbreviations: SD, standard deviation; MRI, magnetic resonance imaging; KOOS, Knee Injury and Osteoarthritis Outcome score; ADL, activities of daily living; QOL, quality of life; IKDC, International Knee Documentation Committee.

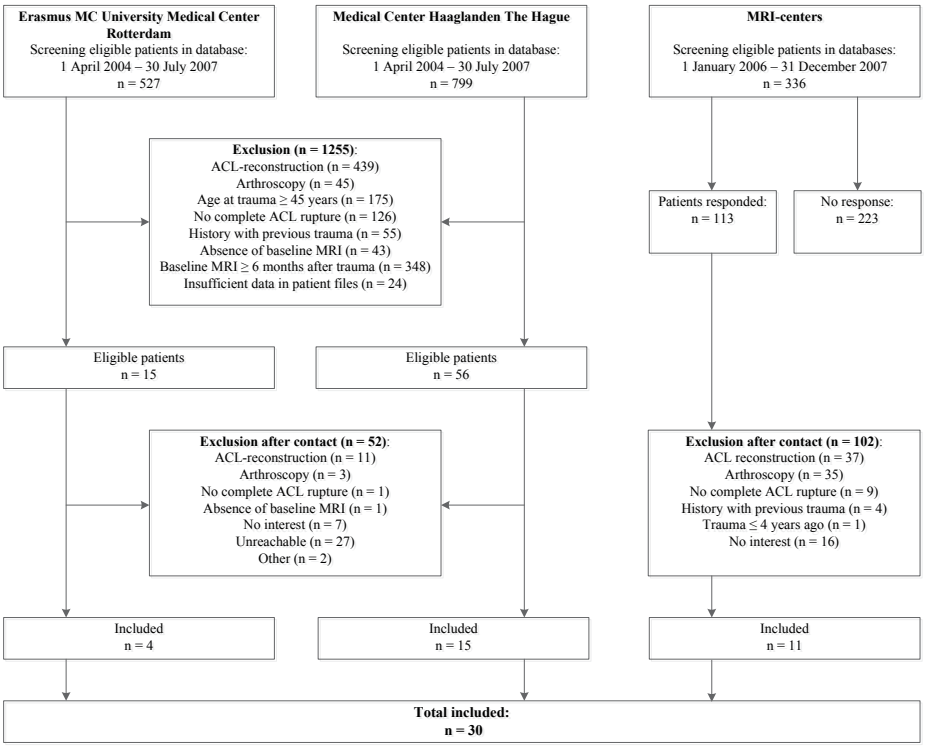

Figure 1. Overview of included patients
Abbreviations; ACL, anterior cruciate ligament; MRI, magnetic resonance imaging.

Inter-rater reliability

Assessment of BMLs in patella, femur, tibia, and the subspinous region showed moderate to good inter-rater reliability, with PABAK values ranging from 0.6 to 1.0. Similarly, for cartilage assessment of the patella, femur, and tibia, PABAK values ranged from 0.6 to 1.0. All locations of osteophytes showed good reliability, with PABAK values ranging from 0.73 to 1.0. The PABAK value for assessment of meniscus morphology was 0.47 for the medial and 0.60 for the lateral meniscus.

OA features assessed with MOAKS

At baseline, many BMLs were scored: in the medial and lateral tibio-femoral compartments > 60% of the patients had BMLs at baseline (Table 2a).

Table 2A. Overview of MOAKS features at baseline and percentage change after 5 years follow-up: Bone marrow lesions and cartilage

	Baseline		**Baseline**		**Change after 5 years**	
	Bone marrow lesion n = 28§		**Cartilage defect n = 30**		**Cartilage defect n = 30**	
	Presence* n (%)	**Presence of cyst n (%)**	**Presence* n (%)**	**Full thickness n (%)**	**Overall (size and% full-thickness together)****	
					Progression (incidence#) n	Improvement n
Patella						
medial	1 (3.6)^	0	2 (6.7)^^	0	5 (4)	0
lateral	0^	0	1 (3.3)^^	0	3 (2)	0
Femur medial						
trochlea	1 (3.6)	0	0	0	0	0
central	14 (50.0)	0	1 (3.3)	0	2 (2)	0
posterior	5 (17.9)	0	0	0	2 (2)	0
Femur lateral						
trochlea	3 (10.7)	0	0	0	0	0
central	14 (50.0)	2 (7.1)	17 (56.7)	7 (23.3)	4 (2)	3
posterior	3 (10.7)	1 (3.6)	2 (6.7)	0	0	0
Tibia medial						
anterior	7 (25.0)	0	1 (3.3)	0	1 (1)	0
central	10 (35.7)	1 (3.6)	1 (3.3)	0	0	0
posterior	10 (35.7)	1 (3.6)	0	0	0	0
Tibia lateral						
anterior	7 (25.0	0	2 (6.7)	0	1 (1)	0
central	19 (67.9)	1 (3.6)	0	0	0	0

Table 2A. Overview of MOAKS features at baseline and percentage change after 5 years follow-up: Bone marrow lesions and cartilage (continued)

	Baseline		**Baseline**		**Change after 5 years**	
	Bone marrow lesion n=28§		**Cartilage defect n=30**		**Cartilage n=30**	
	Presence* n (%)	**Presence of cyst n (%)**	**Presence* n (%)**	**Full thickness n (%)**	**Overall (size and% full-thickness together)****	
					Progression (incidence#) n	Improvement n
posterior	20 (71.4)	0	0	0	0	0
PF	5 (17.9)	0	3 (10.0)	0	7 (5)	0
TF medial	17 (60.7)	2 (7.1)	2 (6.7)	0	5 (5)	0
TF lateral	25 (89.3)	4 (14.3)	18 (60)	7 (23.3)	4 (3)	3

§Presence of bone marrow lesions at baseline could be assessed in 28 patients; 2 MRI scans were unassessable because of insufficient image quality.
*Presence indicates a MOAKS score of size >0.
**If% full-thickness loss had deteriorated, progression was defined, regardless of changes in size of the affected area.
#Incidence of new cartilage defects.
^Patella unassessable (n=1) because of insufficient image quality.
^^No axial sequence and assessed on sagittal sequence (n=14).
Abbreviations: PF, patello-femoral; TF, tibio-femoral.

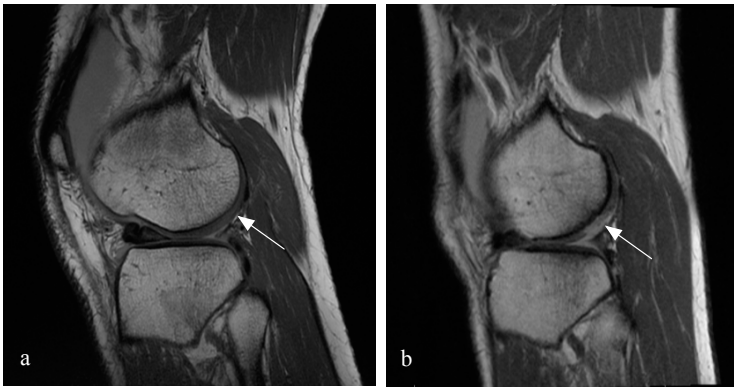

Figure 2. Cartilage progression
a: baseline MRI, cartilage: intact (see arrow)
b: follow-up MRI, cartilage: full thickness defect (see arrow)

Cartilage defects at baseline were scored mainly in the lateral central femur (n=17), of which 7 patients had full-thickness lesions. In total, we scored progression of 16 cartilage defects in 13 patients. Seven patients showed progression of cartilage defects in the patello-femoral compartment at follow-up. Progression of cartilage defects in the medial tibio-femoral compartment was scored in 5 patients and in the lateral tibio-femoral compartment in 4 patients. Example of cartilage progression is shown in figure 2. Three patients showed improvement of the cartilage defect in the central region of the lateral femoral condyle. All other regions showed no improvement at follow-up (Table 2a).

Table 2b shows an overview of the presence of osteophytes in all regions at baseline and the progression after 5 years. In total, 10 patients showed progression of the osteophytes in one (n=6), two (n=3) or three (n=1) compartments.

Table 2B. Overview of MOAKS features at baseline and percentage change after 5 years follow-up: Osteophytes

	Baseline	**Change after 5 years**
	Presence of osteophyte* n (%)	Progression n (incidence#)
Patella		
superior	1 (3.3)	2 (0)
inferior	0	2 (0)
medial**	0	2 (1)
lateral**	0	1 (0)
Femur trochlea		
medial***	0	2 (0)
lateral	0	0
Femur posterior		
medial	0	6 (2)
lateral	0	2 (1)
Femur central		
medial	1 (3.3)	4 (1)
lateral	1 (3.3)	2 (0)
Tibia central		
medial	0	1 (1)
lateral	0	1 (1)
PF	1 (3.3)	4 (1)
TF medial	1 (3.3)	8 (4)
TF lateral	1 (3.3)	3 (2)

*Cut-off point grade ≥ 2.

**Unassessable (n=14) because of absence of axial sequences at baseline.

***Unassessable (n=3) because of significant joint effusion in the knee at baseline.

#Incidence of new osteophytes (from grade 0 to 2).

Abbreviations: PF, patello-femoral; TF, tibio-femoral.

Table 2C. Overview of MOAKS features at baseline and percentage change after 5 years follow-up: Meniscus

	Presence of signal n = 21*	**Tear**	**Morphology change n = 21***		**Extrusion n = 30**		
	T0	**T0**	**T0 versus T5**		**T0**	**Change**	
	n (%)	n (%)	Progr. n (%)	Impr. n (%)	n(%)	Progr. n(%)	Impr. n (%)
Medial							
anterior	0	0	0	0			
body	11 (52.4)	0	4 (19.0)	1(4.8)			
posterior	13 (61.9)	1 (4.8)	4 (19.0)	1(4.8)			
overall	13 (61.9)	1 (4.8)	6 (28.6)	1(4.8)			
central					6 (20.0)	4 (13.3)	3 (10.0)
anterior					20 (66.6)	5 (16.7)	6 (20.0)
Lateral							
anterior	4 (19.0)	3 (14.3)	2 (9.5)	0			
body	5 (23.8)	0	2 (9.5)	0			
posterior	5 (23.8)	4 (19.0)	5 (23.8)	2 (9.5)			
overall	8 (38.1)	6 (28.6)	7 (33.3)	2 (9.5)			
central					1 (3.3)	0	1 (3.3)
anterior					2 (6.7)	0	2 (6.7)

*Unassessable (n = 9), because of a lack of proton density sequences at baseline.
Abbreviations: Impr., improvement; Progr., progression.

Table 3. Overview of changes in cartilage, osteophytes, and meniscus morphology

	Progression n affected/ total (%)	**Improvement n (%)**
Cartilage		
PF	7/30 (23.3)	0
TF medial	5/30 (16.7)	0
TF lateral	4/30 (13.3)	3/30 (10)
Osteophytes		
PF*	4/16 (25.0)	
TF medial	8/30 (26.7)	
TF lateral	3/30 (10.0)	
Meniscus**		
medial	6/21 (28.6)	1/21 (4.8)
lateral	7/21 (33.3)	2/21 (9.5)

*14 patients had no axial MRI sequences at baseline, resulting in no scores for patella medial and lateral.
**9 patients had missing data at baseline because of no proton density weighted MRI sequences at baseline.
Abbreviations: PF, patello-femoral; TF, tibio-femoral.

Percentage of presence of osteophytes at baseline increased if we changed the cut-off point from grade ≥ 2 to grade ≥ 1: patello-femoral compartment, 90% (n=27): medial tibio-femoral compartment, 83.3% (n=25); and lateral tibio-femoral, 66.7% (n=20).

Table 2c shows an overview of the meniscus status at baseline and the change after 5 years. Of the 9 patients without proton density sequences at baseline (not presented in Table 2c), a tear of the medial meniscus was obviously present in 2 patients and of the lateral meniscus in 3 patients. At follow-up, 1 patient showed improvement medially and 2 patients laterally. We could not define progression in these patients because of the lack of proton density sequences at baseline.

An overview of progression and improvement of the features is given in Table 3.

Twenty-one of the 30 patients (70%) showed progression of at least one of the following features: cartilage, osteophytes or meniscus pathology.

OA definition on MRI

At follow-up, 2 patients (6.7%) met the MRI-based definition of patello-femoral OA and 7 patients (23.3%) of tibio-femoral OA. Two patients had both patello-femoral and tibio-femoral OA. Two patients (6.7%) had patello-femoral OA in the contralateral knee and 2 other patients (6.7%) had contralateral tibio-femoral OA. One patient had tibio-femoral OA in both the affected and contralateral knees.

DISCUSSION

In our study of patients 5 years after non-operatively treated ACL rupture, progression of cartilage, osteophytes, or meniscus pathology, assessed with MOAKS, occurred in 70% of the patients. Analyses of each feature separately showed percentages of progression between 10% and 33%. This indicates that involvement of each feature in the degenerative process varied among the patients in our study. Secondly, we found that almost one-quarter of our patients met the MRI-based definition for knee OA and that the tibio-femoral compartment was more frequently affected than the patello-femoral compartment.

Progression of cartilage defects was evident in almost one-quarter of the patients. In all 3 compartments (patello-femoral, tibio-femoral medial and lateral) the progression was mainly caused by the development of new defects occurring during the follow-up period rather than by deterioration of pre-existing lesions. This finding may suggest that kinematics plays a role in the development of degenerative changes. A possible explanation for development of new cartilage defects is the change in load in the ACL-deficient knee. One-third of the patients showed progression of osteophytes.

As expected, at baseline, osteophytes graded ≥ 2 were rare in our study population consisting of young people with no history of OA-related symptoms at the time of trauma. However, osteophytes with grade ≥ 1 were present in each compartment in at least two-thirds of the patients. At baseline, meniscal tears were more often present in the lateral meniscus than in the medial meniscus. Both menisci showed progression in pathology in approximately 30% of the patients.

A striking finding is the improvement of cartilage defects, localized in the central region of the lateral femoral condyle, in 3 patients. We did consider the possibility of different slice selection and partial volume averaging, but after careful examination of the baseline and follow-up MRI images, this was deemed inapplicable in these 3 patients. A possible explanation is that we captured cartilage swelling at follow-up. Previous studies reported both cartilage thickening and thinning measured quantitatively in human knees with radiographic OA.[19] Furthermore, cartilage thickening was found in the external medial and lateral regions of the femur in early radiographic OA.[20] Cartilage thickening may be a protective mechanism against degenerative changes and may be present in the early degenerative process. Another study reported cartilage thickening in the medial part of the femur 2 years after ACL rupture.[21] Similarly, Andreisek et al. found cartilage thickening in the medial femur 7 years after ACL reconstruction. [22] In contrast to the above-mentioned studies, we detected cartilage improvement / thickening only in the lateral femur.

Progression of cartilage and meniscus pathology was not different between the medial and lateral tibio-femoral compartments. We found greater progression of osteophytes in the medial tibio-femoral compartment than in the lateral compartment. Panzer et al.[23] found increased osteophyte formation in all compartments after an ACL rupture compared to the contralateral uninjured knee; however, contrary to our results, in their study the lateral tibio-femoral compartment was affected most.

MOAKS is a relatively new semi-quantitative scoring system. Hunter et al. described this instrument and its reliability in 2011 using MRI data of the OAI Progression subcohort, of which all included knees had a radiographic Kellgren and Lawrence grade of 2 or 3.[12] Our study population consisted of patients with post-traumatic knees, 5 years after ACL rupture, with a different stage of OA: Kellgren and Lawrence grade 0 or 1 (only one patient had grade 2). Therefore, it is difficult to compare our results with the study of Hunter et al., and, to our knowledge, no other studies have reported on similar data assessed with MOAKS. Katz et al.[24] described MOAKS in their rationale and design of the Meniscal Tear in Osteoarthritis (MeTeOR) Trial, in which they intend to apply it for evaluating OA progression based on MRI measurements taken at baseline

and 18 months' follow-up. Apart from the present study, MOAKS is being implemented in a variety of ongoing OA studies at our institution.

Hunter et al.[8] did not describe a definition for determining incidence, progression, or change between two measurements. Therefore, we established our own definitions of progression for each OA feature. However, in our study, we found it difficult to detect more subtle changes when applying repeated scoring with MOAKS. This is especially a problem for within-grade changes of cartilage lesions. For example, if the size of any cartilage loss is between 10% and 75% of the surface area in an individual region, this change is not captured because any lesion with a surface area between 10% and 75% is scored as grade 2. This also applies to BMLs, although we were not able to assess progression of BMLs because of the presence of traumatic BMLs at baseline.

For the definition of OA on MRI, we chose grade 2 as cut-off point for definite osteophytes after consultation with the author of the study in which definition of OA on MRI was first described.[13] One may argue that a cut-off point of grade 1 could be a better indicator for an early degenerative stage. In our population, the percentage of patients with osteophytes at baseline increased enormously after changing the cut-off point from grade 2 to grade 1. In our experience it is difficult to distinguish between grade 0 and grade 1 osteophytes. This is also reflected in the lower PABAK values for the inter-rater reliability; when we used grade 1 as the cut-off point the PABAK values ranged from 0.10 to 0.87 compared to 0.73 to 1 when we used grade 2. Hence, we chose grade 2 as the cut-off point.

The primary strength of our study is its use of a homogeneous patient population; all patients had chronic ACL deficiency, did not receive surgical intervention and were evaluated with the same follow-up period.

Our study also has several limitations. We used a 1.5 Tesla MRI scanner instead of a 3.0 Tesla as described by Hunter et al.[12] Not all patients had axial MRI sequences at baseline and, for some patients, proton density weighted sequences were lacking, resulting in incomplete meniscal scores at baseline. Because of our small sample size we were only able to perform descriptive statistical analyses. We did not analyze the relationship between clinical findings (objective and subjective data) and the changes of MOAKS because of the small sample size.

Although it was difficult to identify patients with a chronic ACL-deficient knee and no surgical interventions for both knees, we chose this population to ensure that development of possible degenerative features was not influenced by surgical procedures. The OA prevalence in our study could be an underestimation of the entire population with ACL rupture, consisting of patients treated operatively with ACL reconstruction and/ or operatively for additional injuries and patients treated non-operatively.

In conclusion, in the present study, MRI identified high percentages of early degenerative changes, which are not detectable on radiographs, in chronic ACL-deficient patients. Five years after ACL rupture, almost one-quarter of non-operatively treated patients met the MRI-based definition for knee OA. The results show that progression of cartilage, osteophytes, or meniscus pathology, assessed with MOAKS, occurred in 70% of the patients. Involvement of each degenerative feature varied per patient.

Finally, our results confirm that MOAKS can detect degenerative changes in ACL-deficient patients, a high-risk group for OA development.

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CHAPTER 7

Degenerative changes of the knee two years after anterior cruciate ligament rupture and related risk factors: a prospective observational follow-up study

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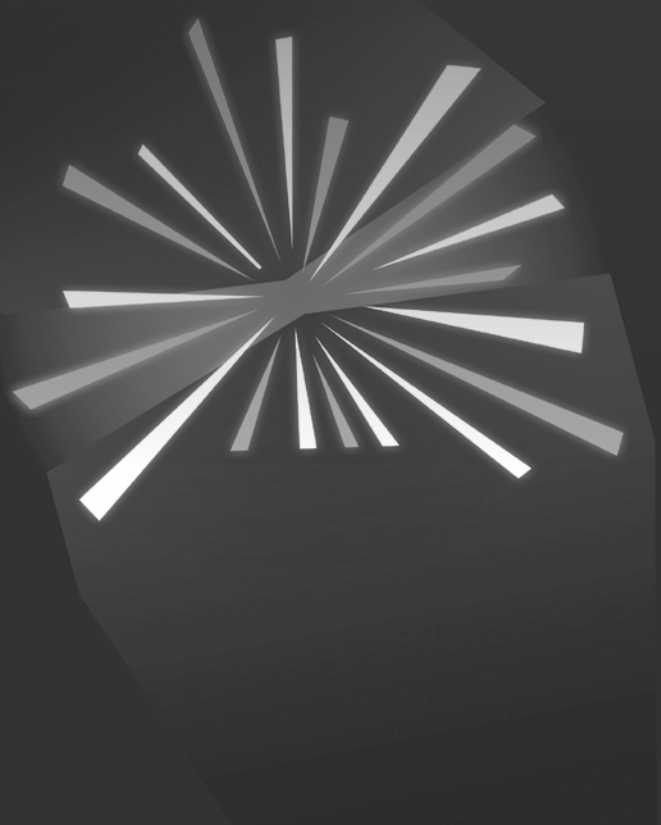
Submitted for publication



ABSTRACT

Purpose: To identify early degenerative changes as assessed on MRI after two-year follow-up in patients with a recent anterior cruciate ligament (ACL) rupture and to evaluate which determinants are related to these changes.

Study design: Prospective observational follow-up study

Methods: 154 adults aged between 18 and 45 years with acute ACL rupture diagnosed by physical examination and MRI, without previous knee trauma or surgery and without osteoarthritic changes on X-ray were included in the study. 143 patients completed the 2-year follow-up. All patients were treated according to the Dutch guideline on ACL injury. Of the 143 patients, 50 patients were treated non-operatively during the 2-year follow-up period. Main outcome was early degenerative changes assessed on MRI defined as progression of cartilage defects and osteophytes in tibiofemoral and patellofemoral compartments. Patient characteristics, activity-level, functional instability, treatment and trauma related variables were evaluated as determinants.

Results: Progression of cartilage defects in medial and lateral tibiofemoral compartments were present in 12% and 27% of patients. Progression of osteophytes in tibiofemoral and patellofemoral compartments were present in 10% and 8% of patients. The following determinants were positively significantly associated with early degenerative changes: male gender (OR 4.43, 95% CI 1.43-13.66, p = 0.010), cartilage defect in medial tibiofemoral compartment at baseline (OR 3.66, 95% CI 1.04-12.95, p = 0.044), presence of bone marrow lesions in medial tibiofemoral compartment (OR 5.19, 95% CI 1.56-17.25, p = 0.007) and joint effusion (OR 4.19, 95% CI 1.05-16.72, p = 0.042) one year after trauma, and presence of meniscal tears (OR 6.37, 95% CI 1.94-20.88, p = 0.002).

Conclusions and Relevance: Two years after ACL rupture early degenerative changes were assessed on MRI. Concomitant cartilage defect and meniscal injury, male gender, persistent bone marrow lesions and joint effusion are risk factors for degenerative changes.

INTRODUCTION

Anterior cruciate ligament (ACL) rupture is a common sports-related injury, with an annual incidence of approximately 5 to 8 per 10,000 persons in the general populations.[1-3] Osteoarthritis (OA) is a well-known, devastating long-term consequence of an ACL rupture. A systematic review showed that the risk of OA in patients with an isolated ACL rupture after a minimal follow-up time of 10 years is low (0%-13%), in contrast to patients with combined injuries (21%-48%).[4] This means that a large percentage of subjects with such combined injuries will develop knee OA at a relatively young age. A meta-analysis of 16 studies with a minimum of 10 years follow-up confirmed that the risk of developing OA after ACL reconstruction increased when meniscectomy was performed.[5] However, not all patients will ultimately develop knee OA after ACL rupture.

Most previous studies reported long-term follow-up of at least 10 years with radiographic OA outcome. In clinical practice, radiography is the most common imaging modality to diagnose OA and evaluate OA patients over time. However, radiography has limited sensitivity for identifying early degenerative changes because it only depicts bony features and joint space width, which are indirect measures of cartilage thickness and meniscus integrity.[6] OA is generally regarded as a disease of the whole joint with involvement of all tissues.[7,8] Hence, MRI has become an important tool for OA research because of its capability to visualise all structures in the knee joint.[6,9]

To change the course of OA in patients after an ACL rupture we need to identify those patients at risk for OA development and subsequently to develop a treatment strategy or to intervene in the progress of degenerative changes in the early stage.

The aim of our study was to identify early degenerative changes as assessed on MRI after two-year follow-up in patients with a recent ACL rupture and to evaluate which determinants are related to these changes.

METHODS

Population and study design

Hundred fifty-four eligible patients were included in the KNee osteoArthritis anterior cruciate Ligament Lesion (KNALL) study between January 2009 and November 2010. The patients were recruited from three hospitals in the Netherlands: Erasmus MC, University Medical Centre Rotterdam, Medical Centre Haaglanden, The Hague and Reinier de Graaf Gasthuis, Delft. The KNALL study is a prospective observational study of patients who visited the outpatient clinic because of suspected ACL rupture within 6 months after knee trauma. Patients were treated operatively or non-operatively in-

dependent of the study, according to the decision of the treating physician according to the Dutch ACL guideline.[10] Inclusion criteria were: age between 18 and 45 years, presence of ACL rupture diagnosed by physical examination and MRI. Patients who did not speak the Dutch language; those with previous ACL injury, meniscus or cartilage damage; those with previous surgery of the involved knee, those with disabling co-morbidity; and those with already osteoarthritic changes on X-ray (Kellgren and Lawrence grade > 0) were excluded. The included patients were evaluated at baseline, after one year, and after two years. Written informed consent was obtained from all included patients and the study was approved by the institutions' Medical Ethics Committees.

MRI evaluation

Of 143 patients MRI data were available of baseline and two-year follow-up (figure 1: overview of included patients). At baseline the MRI scans were acquired on different MRI scanners with a magnetic field strength of 1.0 (n=31), 1.5 (n=98) or 3.0 (n=14) Tesla. At follow-up all MRI scans were acquired on the same type MRI scanner at 1.5 Tesla. A dedicated knee coil was used and the leg of the patients was positioned

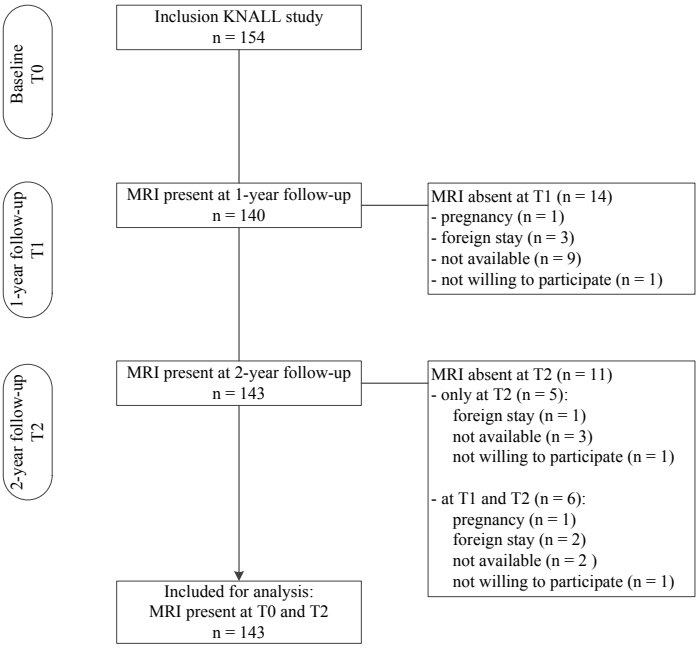


Figure 1. Overview of included patients
Abbreviations: KNALL, KNee osteoArthritis anterior cruciate Ligamen Lesion; MRI, magnetic resonance imaging.

neutrally. MRI examinations included the following MRI pulse sequences: sagittal and coronal proton density weighted turbo spin echo (TSE) sequence (slice thickness 3 mm, TR/TE: 2700/27 ms), coronal T2-weighted TSE sequence with fat saturation (slice thickness 3 mm, TR/TE: 5030/71 ms), axial proton density and T2-weighted TSE sequence (slice thickness 3 mm, TR/TE: 3500/25/74 ms) and sagittal T2 weighted 3D dual steady state (DESS) sequence (slice thickness 1.5 mm, TR/TE 21.35/7.97 ms).

MRI scans were evaluated by an extensively trained physician researcher blinded for clinical information. The baseline and follow-up MRI scans were assessed pair-wise and the order of measurements was known. All MRI scans were evaluated, according to the description of MRI Osteoarthritis Knee Score (MOAKS), as reported by Hunter and colleagues[11]. Briefly, the MOAKS is a semi-quantitative scoring system of structures and features potentially relevant in knee OA. All features are categorised from 0 to 3 or scored as absent/ present. For the present study we combined sub-regions and defined 3 compartments for assessing cartilage, osteophytes and bone marrow lesions (BMLs), namely: patello-femoral (medial and lateral patella, medial and lateral femoral trochlea), medial tibio-femoral (medial femur central and posterior, medial tibia anterior, central and posterior), lateral tibio-femoral (lateral femur central and posterior, lateral tibia anterior, central and posterior). In order to implement the MOAKS adequately all readers of our research team underwent an extensive training program supervised by an experienced musculoskeletal radiologist (10 years of experience).[12]

To assess the reliability in the present study, two readers, the extensively trained physician researcher and the experienced musculoskeletal radiologist independently read MRIs of 15 knees. We determined the Prevalence-Adjusted Bias-Adjusted Kappa (PABAK), which takes into account both the prevalence of a positive finding and bias of each observer for reporting a positive finding and provides therefore a more realistic estimate for agreement than the kappa, if the prevalence of the feature is low.[13] We interpreted the PABAK values the same as kappa values.[14,15] Assessment of BMLs showed moderate to good inter-rater reliability, with PABAK values ranging from 0.73 to 1.0. Similarly, for cartilage assessment, PABAK values ranged from 0.6 to 1.0. Osteophyte scores showed good reliability, with PABAK values ranging from 0.73 to 1.0. The PABAK value for assessment of meniscus morphology was 0.47 for the medial and 0.60 for the lateral meniscus. PABAK value for effusion was 0.73.

Determinants

All included patients were requested to complete several questionnaires. Standardised physical examination and history taking was performed, by one trained MD, at baseline, one- and two-year follow-up. MRI examinations were performed at baseline, one- and two-year follow-up to assess above-mentioned features of the MOAKS. One-year

follow-up measurements were used for assessment of some determinants. We identified the following determinants based on the following hypotheses:

1) Patient characteristics: well-known risk factors for development of OA: gender, age and body mass index (BMI) at baseline;
2) Activity level: the load of the knee before and after ACL trauma may influence the development of degenerative changes. We hypothesised that the pre-trauma Tegner activity score[16] and the average Tegner activity score during the first 2 years post ACL rupture would have a positive relationship with degenerative changes.
3) Frequency of giving way moments was used as a measure for functional instability. The hypothesis was that patients with higher frequency of giving way moments during the first year post ACL rupture would have more degenerative changes. Patients were categorised into 4 groups: 0 times, 1-5 times, 6-12 times and > 12 times.
4) Treatment: the patients were categorised into 3 groups: non-operative, reconstruction < 6 months after ACL rupture and reconstruction ≥ 6 months after ACL rupture. We chose the cut-off point of 6 months as distinction between early and late reconstruction. Graft choice was not included as determinant, a hamstring-tendon graft was used in 93% of the patients.
5) Trauma related variables:

a. Cartilage defect on MRI at baseline in medial and lateral tibiofemoral and patellofemoral compartment (present versus absent). The hypothesis is that presence of cartilage defect at baseline has a positive relationship with early degenerative changes.
b. Joint effusion: we hypothesised that patients who sustained a significant amount of effusion one year after ACL rupture have an increased risk of development of degenerative changes. We analysed the influence of amount of effusion measured at MRI at one-year follow-up. According to the MOAKS effusion was scored in 4 categories from normal to large, for the analyses we defined two categories: normal and small versus medium and large.
c. Presence versus absence of BMLs on MRI at one-year follow-up in three compartments (medial and lateral tibiofemoral and patellofemoral): the hypothesis regarding traumatic BMLs is that presence of BMLs one year after ACL rupture may influence development of degenerative changes.
d. Meniscal tears: 1) presence of meniscal tear at all measurements, because small peripheral tears may heal and disappear on MRI during follow-up and presence from trauma means exposure of minimal 2 years, or presence of meniscal tear at baseline and one-year follow-up and meniscectomy in the second follow-up year; 2) presence of meniscectomy in the first 12 months after ACL rupture.

Outcome measures

We composed the following definitions for early degenerative changes of the MOAKS features.[12]

Cartilage

Progression of cartilage defects was present if the score of area of cartilage defect (size) and/ or% full thickness loss at follow-up was larger than at baseline. Subsequently, the progression measures, size and% full thickness loss, were combined. The following principles were leading for the overall definition: if% full thickness loss had deteriorated, this was defined as progression, regardless of changes in size of affected area; if% full thickness loss had improved, this indicated improvement, irrespective of changes in size of affected area; if% full thickness loss had remained the same, the change of the overall definition was equal to the change of size of affected area. So, if new cartilage defects had developed after 2 years, i.e. from no cartilage defect at baseline to a defect at follow-up, then this was also defined as progression.

Osteophytes

Progression was defined as change of osteophyte grade 0 or 1 at baseline to grade 2 or 3 at follow-up or from grade 2 to 3. Changes of grade 0 to 1 or grade 1 to 0 were defined as no change.

For the analyses we reported progression of cartilage defects in the tibiofemoral medial, tibiofemoral lateral, tibiofemoral medial and lateral combined and patellofemoral compartments, and progression of osteophytes in the tibiofemoral (medial and lateral combined) and patellofemoral compartments.

Statistical Analysis

Descriptive statistics were used to describe baseline characteristics, distribution of determinants and degenerative change at two year of follow-up. Continuous variables were tested for normality. Median and interquartile range (IQR) were obtained for non-normally distributed variables. Primary analyses were performed with univariable logistic regression analyses using the defined early degenerative changes as the dependent variables. Determinants with p values < 0.15 were used in a multivariable model. Logistic regression analyses were used to calculate odds ratios (OR) and 95% confidence intervals (95% CI). For the clinical implication we calculated the positive predictive values for the determinants that had a significant relationship in the multivariable model with the progression of cartilage defects. Statistical analyses were performed with PASW Statistics 20.0 (SPSS Science Inc., Chicago, USA). Significance was tested for p-value < 0.05.

RESULTS

Of the 143 patients of whom MRI data was available at baseline and two-year follow-up, the baseline characteristics are presented in Table 1.

During the 2-year follow-up period an ACL reconstruction was performed in 93 of the 143 patients (65%). Hamstring-tendon graft was used in 87 patients (94%), bone-patellar bone-tendon graft in 4 patients (4%), and a combination of hamstring-tendon and allograft in 2 patients (2%). The median time between trauma and reconstruction was 5.5 (IQR 3.3 to 8.9) months. Partial meniscectomy in the first 12 months after ACL rupture was performed medially in 4 (3%) patients and laterally in 17 (12%) patients. Characteristics of determinants and baseline data of the outcome variables assessed on MRI are presented in Table 2.

Progression or new cartilage defects in the medial tibiofemoral compartment was present in 11.9% (17/143) of the patients, in the lateral tibiofemoral compartment in 26.6% (38/143) of the patients and in the patellofemoral compartment in 2.8% (4/143) of the patients. Progression of cartilage defects in the tibiofemoral compartment (medial and lateral together) was present in 33.6% (48/143) of the patients. Progression of osteo-

Table 1. Baseline characteristics

Characteristic	**n = 143**
Age (years)	25.2 (21.4-32.6)
Gender (female) - *n (%)*	49 (34.3)
BMI (kg/m^2)	23.9 (22.0-26.2)
Injured side (right) - *n (%)*	76 (53.1)
Tegner score pre trauma	9 (7-9)
Time between trauma and MRI at baseline, months	1.0 (0.5-1.9)
Lachman test - *n (%)*	
1+	22 (15.4)
2+	114 (79.7)
3+	7 (4.9)
Lachman test; soft end point - *n (%)*	135 (94.4)*
Pivot shift - *n (%)*	
Normal	43 (30.1)
Glide	65 (45.5)
Clunk	18 (12.6)
Not applicable#	17 (11.9)
KT-1000 arthrometer index knee (maximal manual in mm)	12.0 (10.0-13.0)

Data are presented as median (interquartile range), unless otherwise indicated.
Abbreviations: BMI, body mass index.
*Firm end point: n = 8 (2+, n = 2; 1+, n = 6).
#Not applicable because of opposing muscle contraction

Table 2. Overview outcome variables at baseline and determinants

Outcome variable or determinant	n (%)
Osteophytes at T0	
Patellofemoral	
Grade 0	101 (70.6)
Grade 1	39 (27.3)
Grade 2	3 (2.1)
Tibiofemoral medial	
Grade 0	115 (80.4)
Grade 1	24 (16.8)
Grade 2	4 (2.8)
Tibiofemoral lateral	
Grade 0	124 (86.7)
Grade 1	18 (12.6)
Grade 2	1 (0.7)
Cartilage defect presence at T0	
Patellofemoral	51 (35.7)
Tibiofemoral medial	20 (14.0)
Tibiofemoral lateral	84 (58.7)
Tibiofemoral (medial and/or lateral)	87 (61)
Treatment	
Reconstruction	93 (65)
Non-operative	50 (35)
Time trauma-reconstruction in months (n=93) - *median (IQR)*	5.5 (3.3-8.9)
Non-operative	50 (35)
Reconstruction < 6.0 months	50 (35)
Reconstruction ≥ 6.0 months	43 (30)
Average Tegner activity score during 2-year follow-up – *mean (SD)*	6.3 (1.8)
Giving way moments during first year follow-up*	
0	42 (30)
1-5 times	57 (41)
6-12 times	17 (12)
>12 times	23 (17)
Effusion on MRI at T1**	
Physical amount + small	115 (85)
Medium + large	20 (15)
Bone marrow lesion at T1**	
Patellofemoral	7 (5)
Tibiofemoral medial	27 (20)
Tibiofemoral lateral	25 (19)
Tibiofemoral (medial and/or lateral)	40 (30)
Meniscal tear at all measurements	
Medial	9 (6)
Lateral	10 (7)
Medial and/or lateral	17 (12)
Meniscectomy in 1st 12 months after ACL trauma	21 (15)
Medial/ lateral	4 (3) / 17 (12)
Time between trauma and meniscectomy – *mean (SD)*	6.3 (2.9)

*Missing n = 4, no information at T0 and T1.

**Missing n = 8, no MRI examination at T1.

Abbreviations: ACL, anterior cruciate ligament; IQR, inter quartile range; SD, standard deviation; T0, baseline measurement; T1, one-year follow-up measurement.

phytes in the tibiofemoral compartment was present in 9.8% (14/143) of the patients, and progression of osteophytes in the patellofemoral compartment was present in 7.7% (11/143) of the patients. In total, progression of cartilage defects and/ or osteophytes in any compartment were present in 39.9% (57/143) of the patients.

Because only 2.8% of the patients had progression or new cartilage defects in patellofemoral compartment, we did not analyse the relation between progression of cartilage defects in the patellofemoral compartment and determinants.

In the multivariate analyses, six determinants were significantly related to progression of cartilage defects and osteophytes. Cartilage defect at baseline in the medial tibiofemoral compartment (OR 3.66, 95% CI 1.04 to 12.95, p=0.044), presence of BMLs in the medial tibiofemoral compartment one year after ACL rupture (OR 5.19, 95% CI 1.56 to 17.25, p=0.007) and presence of medial meniscal tear (OR 8.56, 95% CI 1.58 to 46.49, p=0.013) had a significant positive relationship with progression of cartilage defects in the medial tibiofemoral compartment. Male gender (OR 4.43, 95% CI 1.43 to 13.66, p=0.010) and presence of lateral meniscal tear (OR 11.20, 95% CI 2.26 to 55.53, p=0.003) were positively related to progression of cartilage defects in the lateral tibiofemoral compartment. Presence of joint effusion one year after ACL rupture (OR 4.19, 95% CI 1.05 to 16.72, p=0.042) had a positive significant relationship with progression of osteophytes in the tibiofemoral compartment. When progression of cartilage defects in the tibiofemoral compartment (medial and lateral together) was analysed, only meniscal tear, medial and/ or lateral showed a significant positive relationship (OR 6.37, 95% CI 1.94 to 20.88, p=0.002). No other defined determinants were related to early degenerative changes. An overview of the relationships between the determinants and progression of cartilage defects and osteophytes are presented in Tables 3 and 4.

For the significant determinants after multivariable analyses the positive predictive values for progression of cartilage defects are listed in Table 5.

Table 3. Relationship determinants and progression cartilage defects

	Tibiofemoral medial compartment OR (95% CI)		**Tibiofemoral lateral compartment OR (95% CI)**		**Tibiofemoral (medial and lateral) compartment OR (95% CI)**	
Determinants	univariable	multivariable*	univariable	multivariable*	univariable	multivariable*
Age at T0	0.97 (0.89; 1.04)		1.01 (0.95; 1.06)		0.99 (0.95; 1.04)	
Male gender	1.29 (0.43; 3.89)		**2.95 (1.19; 7.32)**	**4.43 (1.43; 13.66)**	**2.65 (1.18; 5.94)**	2.40 (0.99; 5.83)
BMI at T0	1.05 (0.92; 1.19)		0.98 (0.89; 1.09)		0.99 (0.90; 1.09)	
Tegner activity score pre-trauma	0.99 (0.70; 1.39)		1.20 (0.91; 1.59)		1.15 (0.89; 1.47)	
Cartilage defect PF at T0	1.31 (0.46; 3.67)		1.46 (0.68; 3.11)		1.48 (0.72; 3.02)	
Cartilage defect TFmed at T0	**4.36 (1.40; 13.64)**	**3.66 (1.04; 12.95)**	1.22 (0.43; 3.44)			
Cartilage defect TFlat at T0	0.77 (0.28; 2.11)		1.29 (0.60; 2.76)			
Cart defect TF at T0					1.11 (0.54; 2.27)	
Mean Tegner activity score during 2-year follow-up	0.84 (0.63; 1.13)		1.06 (0.86; 1.31)		1.02 (0.84; 1.24)	
Givingway moments during 1st follow-up year**						
0 times	1		1		1	
1-5 times	0.84 (0.26; 2.71)		1.10 (0.49; 2.70)		1.08 (0.47; 2.51)	
6-12 times	0.38 (0.04; 3.38)		0.87 (0.23; 3.23)		0.62 (0.17; 2.24)	
12 times	0.90 (0.20; 3.99)		0.78 (0.23; 2.62)		1.07 (0.37; 3.11)	
Effusion at T1*	1.39 (0.36; 5.38)		*2.07 (0.77; 5.58)*	2.11 (0.73; 6.11)	*2.29 (0.87; 5.98)*	2.31 (0.82; 6.48)
BML PF at T1*	1.26 (0.14; 11.16)		1.11 (0.21; 5.97)		1.54 (0.33; 7.18)	
BML TFmed at T1*	**5.26 (1.76; 15.75)**	**5.19 (1.56; 17.25)**	0.95 (0.37; 2.49)			
BML TFlat at T1*	1.02 (0.27; 3.88)		1.73 (0.69; 4.36)			
BML TF at T1*					*2.06 (0.96; 4.43)*	2.13 (0.92; 4.92)

Table 3. Relationship determinants and progression cartilage defects (continued)

	Tibio-femoral medial compartment OR (95% CI)		**Tibio-femoral lateral compartment OR (95% CI)**		**Tibio-femoral (medial and lateral) compartment OR (95% CI)**	
Determinants	univariable	multivariable*	univariable	multivariable*	univariable	multivariable*
Treatment:						
non-operative	1		1		1	
reconstruction < 6.0 months	1.17 (0.39; 3.52)		0.53 (0.21; 1.32)		0.64 (0.28; 1.47)	
reconstruction ≥ 6.0 months	0.30 (0.06; 1.53)		0.82 (0.34; 2.01)		0.65 (0.27; 1.54)	
Medial meniscal tear at all measurements	*4.29 (0.96; 19.06)*	**8.56 (1.58; 46.49)**	2.35 (0.60; 9.27)			
Lateral meniscal tear at all measurements	1.97 (0.38; 10.14)		**4.73 (1.26; 17.83)**	**11.20 (2.26; 55.53)**		
Meniscal tear at all measurements					**3.31 (1.17; 9.34)**	**6.37 (1.94; 20.88)**
Meniscectomy 1st 12 months after ACL trauma	1.29 (0.34; 4.93)		0.61 (0.19; 1.94)		0.99 (0.37; 2.64)	

*Missing n = 8: no MRI examination at T1.

**Missing n = 4: no information about giving way moments at T0 and T1.

Abbreviations: OR: odds ratio; CI: confidence interval; T0: baseline measurements; T1: one-year follow-up measurement; BMI: body mass index; ACL: anterior cruciate ligament; PF: patello-femoral compartment; TF: tibio-femoral compartment; TFmed: medial tibio-femoral compartment; TFlat: lateral tibio-femoral.

Data with p-values < 0.05 are printed in bold; data with p-values < 0.15 in univariable model are printed in italic.

Table 4. Relationship determinants and progression osteophytes

	Tibiofemoral (medial and lateral) compartment OR (95% CI)		**Patellofemoral compartment OR (95% CI)**	
Determinants	univariable	multivariable*	univariable	multivariable*
Age at T0	0.95 (0.87; 1.04)		0.95 (0.86; 1.05)	
Male gender	2.03 (0.54; 7.66)		1.43 (0.36; 5.64)	
BMI at T0	1.08 (0.95; 1.24)		0.86 (0.69; 1.08)	
Tegner activity score pre-trauma	*1.65 (0.96; 2.82)*	1.76 (0.93; 3.33)	1.40 (0.82; 2.38)	
Cartilage defect PF at T0	0.70 (0.21; 2.35)		0.38 (0.08; 1.81)	
Cartilage defect TFmed at T0	1.80 (0.45; 7.11)		2.54 (0.61; 10.51)	
Cartilage defect TFlat at T0	**4.75 (1.02; 22.09)**	4.50 (0.89; 22.73)	1.25 (0.35; 4.48)	
Mean Tegner activity score during 2-year follow-up	1.07 (0.78; 1.47)		1.26 (0.87; 1.82)	
Givingway moments during 1st follow-up year**				
0 times	1		1	
1-5 times	0.56 (0.14; 2.22)		0.72 (0.17; 3.05)	
6-12 times	0.46 (0.05; 4.28)		1.27 (0.21; 7.66)	
>12 times	1.11 (0.24; 5.13)		0.43 (0.05; 4.11)	
Effusion at T1*	**3.93 (1.16; 13.29)**	**4.26 (1.07; 16.90)**	1.31 (0.26; 6.56)	
BML PF at T1*	0.00 (0.00; .)		1.97 (0.22; 17.99)	
BML TFmed at T1*	1.10 (0.29; 4.26)		0.88 (0.18; 4.33)	
BML TFlat at T1*	0.71 (0.15; 3.39)		0.98 (0.20; 4.82)	
Treatment:				
non-operative	*1*	1	*1*	1
reconstruction < 6.0 months	*7.98 (0.94; 67.46)*	3.46 (0.36; 33.35)	*7.98 (0.94; 67.46)*	6.13 (0.69; 54.59)
reconstruction ≥ 6.0 months	*7.95 (0.92; 68.87)*	6.07 (0.65; 56.71)	*3.68 (0.37; 36.71)*	2.96 (0.29; 30.74)

Table 4. Relationship determinants and progression osteophytes (continued)

	Tibiofemoral (medial and lateral) compartment OR (95% CI)		**Patellofemoral compartment OR (95% CI)**	
Determinants	univariable	multivariable*	univariable	multivariable*
Medial meniscal tear at all measurements	1.16 (0.14; 10.05)		0.00 (0.00;.)	
Lateral meniscal tear at all measurements	1.03 (0.12; 8.75)		1.37 (0.16; 11.90)	
Meniscectomy 1st 12 months after ACL trauma	*2.64 (0.74; 9.35)*	1.46 (0.35; 6.04)	**3.87 (1.02; 14.61)**	2.61 (0.66; 10.34)

*Missings n = 8, no MRI examination at T1.

**Missings n = 4, no information about giving way moments at T0 and T1.

Abbreviations: ACL, anterior cruciate ligament; BMI, body mass index; BML, bone marrow lesion; CI, confidence interval; T0, baseline measurement; T1, one-year follow-up measurement; OR, odds ratio; PF, patellofemoral compartment; TF, tibiofemoral compartment; TFmed, medial tibiofemoral compartment; TFlat, lateral tibiofemoral.

Data with p-values < 0.05 are printed in bold; data with p-values < 0.15 in univariable model are printed in italic.

Table 5. Positive predictive values of cartilage defect progression

		Progression cartilage defects in medial tibiofemoral compartment			Progression cartilage defects in lateral tibiofemoral compartment			Progression cartilage defects in tibiofemoral compartment		
		Prior chance: 12% (17/143)			Prior chance: 27% (38/143)			Prior chance: 34% (48/143)		
		yes	no	**PPV**	yes	no	**PPV**	yes	no	**PPV**
Gender	male				31	63	**0.33**			
	female				7	42				
Cartilage defect TFmed at T0	yes	6	14	**0.30**						
	no	11	112							
BML TFmed at T1*	yes	8	19	**0.30**						
	no	8	100							
Medial meniscal tear at all measurements	yes	3	7	**0.30**						
	no	14	119							
lateral meniscal tear at all measurements	yes				6	4	**0.60**			
	no				32	101				
meniscal tear at all measurements	yes							10	7	**0.59**
	no							38	88	

*Missings n = 8, no MRI examination at T1.
Abbreviations: BML, bone marrow lesion; PPV, positive predictive value; T0, baseline measurement; T1, one-year follow-up measurement; TF, tibiofemoral compartment; TFmed, medial tibiofemoral compartment.

DISCUSSION

The results of this prospective observational study showed that two years after ACL rupture early degenerative changes as progression of cartilage defects or osteophytes were present in more than one-third of the patients. Progression of cartilage defects in the tibiofemoral compartment were positively related to cartilage defects in the medial tibiofemoral compartment visualised shortly after ACL rupture, presence of BMLs in the medial tibiofemoral compartment one year after ACL rupture, presence of medial and/ or lateral meniscal tears and male gender. Progression of osteophytes in the tibiofemoral compartment was associated with presence of joint effusion one year after ACL rupture. None of the determinants were associated with progression of osteophytes in patellofemoral compartment.

In our study, the early degenerative changes manifested mainly as progression of cartilage defects. A recent systematic review of longitudinal MRI studies studying cartilage

degeneration confirmed that macroscopic cartilage changes were detectable as early as 2 years following ACL rupture and reconstruction.[17] Similar to our results, these studies found a strong to moderate evidence for influence of meniscal injuries and presence of initial BMLs on cartilage changes.[17] The important role of concomitant meniscal injuries in the degenerative process is in accordance with the conclusions of previous published systematic reviews which included long-term follow-up studies of at least 10 years.[4,18] Meniscectomy is also a well-studied determinant that has a strong relationship with increased risk of developing OA.[4,5] However, our results did not show a relationship between meniscectomy and early degenerative changes in the 2-year follow-up period. We included only patients in the meniscectomy group if they underwent meniscectomy in the first year after inclusion to guarantee a minimal exposure time of one year before assessment of degenerative changes at two-year follow-up. The mean time of exposure of meniscal resection was 21 months. An explanation might be that in this study exposure of meniscal resection during a period of minimal one and maximal 2 years was too short for development of degenerative changes.

Traumatic BMLs represent a footprint of the ACL injury mechanism, located primarily in the lateral femoral condyle and the postero-lateral tibia plateau.[19] Reported resolving time of post-traumatic BMLs varied between 6 months and more than 2 years.[20-24] In our study, the majority (70%) of the BMLs in the tibiofemoral compartment were resolved within one year. After one year we found no new BMLs in the lateral compartment, however at the 2-year follow-up measurement 10 of the 27 patients developed new BMLs compared to the one-year follow-up. This is in accordance with the finding that new BMLs developed in a third of the knees over a two-year period in a prospective follow-up study of patients after acute ACL rupture.[25] Our findings are consistent with the report of Koster et al.[26] They found that presence of bone marrow lesions in the tibiofemoral compartment after knee injury was a strong predictor for new onset or progression of knee OA after one-year follow-up.[26] However, we found a significantly positive relationship between presence of BMLs and early degenerative changes only in the medial tibiofemoral compartment. A total of 27 patients had BMLs in the medial tibiofemoral compartment one year after ACL rupture, of which 7 patients had new lesions compared to baseline. We could not distinguish whether the 7 new BMLs at one-year follow-up were trauma-related or degenerative-related BMLs.

Our results showed that joint effusion one year after ACL trauma had a significant relationship with progression of osteophytes in the tibiofemoral compartment and a borderline significant relationship with progression of cartilage defects in this compartment. Presence of effusion one year after ACL trauma could be an indirect effect of synovitis. This inflammatory process may play a role in initiating degenerative changes. This was confirmed in a subcohort of the MOST study, in which presence of effusion

/ synovitis at baseline was a predictor for future cartilage loss in knees without radiographic OA at baseline.[27]

The choice of treatment was not related with degenerative changes, in accordance with longer follow-up studies.[28-32]

It could be that we are still not able to restore the natural tibiofemoral kinematics after ACL reconstruction despite of developments of new ACL reconstruction techniques. After ACL reconstruction the anteroposterior translation decreases, but subluxation of the tibia could remain.[33,34] This subluxation might be subtle, because we found no association between giving way moments during the first year after ACL rupture and early degenerative changes in our study.

In contrast to other studies[31,35-41] well-known risk factors for OA, such as age and BMI were not associated with early degenerative changes. We must point out that our population was young and had normal BMIs. Our results showed that males were more at risk for development of early degenerative changes than females, although female sex is associated with higher prevalences of OA in the literature[42] However, the association between male sex and progression of cartilage defect was only found in in the lateral tibiofemoral compartment and the association with the whole tibiofemoral (medial and lateral together) compartment was weaker.

In general, medial compartment OA is more common than lateral compartment OA.[43]. Increased weight bearing of the medial compartment compared to the lateral compartment, also caused by varus malalignment and obesity, might cause this finding.[44] However, in post-traumatic populations it has been shown that degenerative changes were more common in the lateral compartment[45,46], and this may explain the finding of more early degenerative changes in the lateral than medial compartment in our study. This could be related to the initial trauma and the concomitant BMLs and cartilage defects predominantly in the lateral compartment as we found in our study. Another explanation might be the change in loading pattern in the lateral compartment after ACL rupture.[34,47,48] We found fewer early degenerative changes in the patellofemoral compartment than in the tibiofemoral compartment. However, at mid- and long-term follow-up after ACL reconstruction patellofemoral OA occurs as often as tibiofemoral OA. Besides, it seems that the prevalence of patellofemoral OA increases with time after reconstruction surgery.[49]

A strength of our study is that determinants, which could be considered as risk factors, were studied in a prospective follow-up study and were analysed using multivariable regression, as advised in literature.[4] This study population is an important target group in

OA research because the patients are young and are at risk for developing OA at young age resulting in long-lasting medical consumption. Additional strength of our study is the use of MRI for determination of early degenerative changes. Using this imaging modality we were able to evaluate all tissues into the knee joint and pre-radiographic degenerative changes could be visualised in an early stage.[6]

This study had also some limitations. Some patients underwent already a MRI scan before assessment of eligibility for the study, resulting in the use of different MRI scanners varying from 1.0 to 3.0 Tesla. The use of the Tegner acticity score as measurement for activity and knee loading is debatable. This questionnaire is a knee related activity scale where work and sport activities are graded on a scale between 0 and 10. We had no information concerning the loads on the injured and contralateral knee separately. So, Tegner activity score is a gross measurement for knee loading. Secondly, the MOAKS was primarily developed for determination of the OA status, since assessment of longitudinal follow-up and changes were not described.[11] Therefore, we defined definitions of progression and improvement of the main MOAKS features.[12] As discussed in the study of Runhaar et al.[12] we were unable to score within-grade progression or improvement of certain features, as changes in grades with a wide range of severity, e.g. grade 2 for size and full-thickness percentage of cartilage defect: 10%-75% of surface area, are not express in the score. Concerning assessment of the meniscus, in the analyses we did not distinct between the different types of tears because of the small amount of scored tears. Visual differentiation on MRI between partial meniscectomy and maceration is not possible. Therefore, we used surgical data for information about the type of meniscectomy performed. We did not incorporated meniscal repair in the analyses, because only 8 patients were documented with a meniscal repair during the 2-year follow-up period.

Conclusions and clinical implications

Two years after ACL rupture early degenerative changes were seen especially as a progression of cartilage defects in the lateral tibiofemoral compartment. Important findings for clinical practice are that the risk of cartilage progression in the medial tibiofemoral compartment increased from 12 to 30% in patients with concomitant cartilage defects in the medial tibiofemoral compartment at baseline, concomitant medial meniscal tear or persistent BMLs in the medial tibiofemoral compartment. The risk of cartilage progression in the lateral tibiofemoral compartment increased from 27% to 33% in males and the risk increased from 27% to 60% in patients with a lateral meniscal tear. Presence of medial and/ or lateral meniscal injury caused an increase of risk from 34% to 59% for development of cartilage progression in the tibiofemoral compartment.

For adequate interpretation of these positive predictive values, it should be noted that these values have confidence intervals influenced by the number of patients.

Attention to above-mentioned risk factors might contribute to development of disease modifying OA drugs, but also to development of more applicable treatment options, such as adaptation of mechanical load or extra strengthening of the surrounded muscles during rehabilitation. Besides, assessment of early degenerative changes can be used as intermediate outcome for evaluating the effect of interventions after ACL rupture resulting in shorter follow-up of longitudinal studies. Mid- en long-term monitoring of the KNALL cohort, as well as additional prospective cohorts of patients with an ACL rupture must contribute to further knowledge of the changes that occur in the knee joint after ACL rupture.

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CHAPTER 8

General Discussion

This thesis attempts to recognize early changes in the knee after an anterior cruciate ligament (ACL) rupture and to study which determinants are related to early degenerative changes.

Our systematic review (Chapter 2) showed that a lot of studies reported risk factors for development of osteoarthritis (OA) after ACL rupture. Most studies investigated mid- and long-term outcome, few studies focused on early degenerative changes. The results showed that for many determinants, limited evidence and conflicting evidence was found. The methodological quality, of the studies according to the risk of bias assessment, was low. More high-quality prospective studies are needed to evaluate determinants and their role in the development of knee OA after ACL rupture. To understand the processes in the knee after an ACL rupture and possibly to adapt the rehabilitation, it is important to investigate the changes and the influence of different determinants in the first years after trauma. The challenge is to identify, shortly after ACL rupture, those patients at high risk for development of knee OA. For identification of these changes and evaluation of its related determinants we designed a prospective observational study in which patients with an acute ACL rupture were included and were evaluated during two-year follow-up (KNALL study). The main findings from the KNALL study were that two years after ACL rupture degenerative changes, as assessed on MRI in the knee, were identified in more than one-third of the patients. The related risk factors were concomitant meniscal injury, concomitant cartilage defect in the medial tibiofemoral compartment, presence of bone marrow lesions in the medial tibiofemoral compartment and effusion one year after ACL rupture. Choice of treatment had no relationship with degenerative changes after 2-year follow-up. (Chapter 7) Bone mineral density values in both tibial and femoral regions were lower in the injured knee than in the contralateral knee shortly after ACL rupture and during two-year follow-up. BMD values in the operatively treated patients decreased in the first follow-up year and increased in the second follow-up year. (Chapter 5)

IDENTIFICATION OF EARLY DEGENERATIVE CHANGES

Most mid- and long-term outcome studies used radiographic scoring systems for evaluating development and progression of OA (Chapter 2). It is difficult to compare studies because of the use of different scoring systems and cut-off values for OA. For identification of early degenerative changes, radiographic evaluation is not useful because only bony changes and joint space narrowing, as indirect measures of cartilage thinning and meniscus integrity, could be visualized.[1] Different MRI techniques, semi-quantitative and quantitative scoring methods, are available for visualisation of all tissues in the

knee involved in the OA process.[1,2] For evaluating early degenerative changes in this thesis we used the semi-quantitative scoring method MRI OsteoArhritis Knee Score (MOAKS).[3] We chose for this scoring method, because it was an improved modified version of the Whole-Organ Magnetic Resonance Imaging Score (WORMS)[4] and Boston Leeds Osteoarthritis Knee Score (BLOKS)[5] After we finished scoring the MRI's and analysing our results, recently a new semi-quantitative MRI scoring method was published that is applicable for acute ACL injury and longitudinal follow-up. The Anterior Cruciate Ligament OsteoArthritis Score (ACLOAS) was developed based on especially the WORMS and MOAKS.[6] In addition to these existing scoring methods, the ACLOAS includes a detailed assessment of the baseline injury pattern, assessment of ligaments, the ACL graft and indirect MRI signs of instability. Besides, a differentiation between traumatic and degenerative BMLs is introduced in the ACLOAS.[6] Further validation of the ACLOAS should be performed. For assessing changes in the knee joint during follow-up we defined progression of the different MOAKS features.[7] A disadvantage of our used scoring method is the lack of determining within-grade progression. It has been shown that within-grade changes in semi-quantitative MRI assessment increase the sensitivity for longitudinal changes during follow-up.[8] Thus, subtle changes during the 2-year follow-up could not be identified with the MOAKS. At follow-up measurements we did not distinct between traumatic and degenerative BMLs, as the ACLOAS does. However, it is doubtable whether it is possible to make a distinction between traumatic and degenerative BMLs in the first years after ACL rupture, when patients might experience giving way moments. It is described that degenerative related BMLs are circumscript, located more subchondral, may have cystic components and are related to cartilage defects. Traumatic related BMLs are less circumscript, more diffuse and described as heterogeneous signal alterations.[9] Based on our experience of scoring BMLs in ACL patients, it might be possible that degenerative BMLs are not recognizable as such or we are not able to distinguish them from the acute traumatic BML after ACL rupture due the enormous impact of the injury resulting in diffuse high-signal alterations on MRI. Another question is how to define BMLs around a cartilage defect in the lateral-posterior region of the knee one year after ACL rupture. These BMLs may be degenerative or a sequel of traumatic BML after a high impact giving way moment. Besides, we do not know if BMLs during follow-up moved within the same subregion. However, in chapter 6 we demonstrated that the MOAKS could detect degenerative changes in chronic ACL-deficient patients.

In this thesis we used a semi-quantitative MRI scoring method for identification of morphological changes in the knee. Quantitative MRI assessment for thickness and volume of different tissues (e.g. cartilage, bone marrow lesions, menisci) is also commonly used in scientific OA research.[1,10-12] An advantage of semi-quantitative scoring

compared to quantitative scoring is the use of conventional MRI's without additional techniques for quantification. However semi-quantitative scoring methods are more observer-dependent than quantitative scoring methods. Both techniques have shown to be reliable and sensitive for detecting structural changes on MRI.[2] Compared to the above mentioned techniques for identification of morphological changes, more advanced MRI techniques can be used for quantitative assessment of biochemical composition of cartilage, such as dGEMRIC (delayed gadolinium enhanced MRI of cartilage), T2 and T1rho mapping. These novel methods are sensitive to subtle biochemical changes of cartilage in the early phase. Studies using quantitative MRI methods showed that within weeks of an ACL rupture the biochemical composition of cartilage was changed and that this damage persists one year after initial trauma.[13] Difficulties and disadvantages to implement quantitative scoring methods in the clinical setting are the costs, the use of contrast (dGEMRIC), the availability of specific MRI pulse sequences (T1rho mapping) and its long examination time. Although, these techniques are used in small cohorts, it can add valuable information to the knowledge of the changes in the knee after ACL rupture.

DETERMINANTS

Isolated ACL rupture occurs rarely, and associated injuries, such as meniscal tears, cartilage lesions, other ligament injuries and bone bruises are common.[14-16]

Meniscal injury

It is well known that the main functions of the menisci are shock absorption and load spreading during movement of the knee joint and static loading. After meniscectomy the contact area decreases and contact pressure increases, medial meniscectomy results in 100% increase of contact stress and lateral meniscectomy results in 200% to 300% increase of contact stress, so the underlying cartilage area will be focally over loaded.[17,18] Besides, the meniscus also contributes to joint stability, diminishing both anterior-posterior translation and rotational stability.[19-21] Proprioception of the knee joint is also mediated by mechanoreceptors that are present in the anterior and posterior horns and outer third of the body of the menisci.[22] Partial meniscectomy resulted in a poorer knee joint position sense compared to healthy controls.[23]

This thesis confirmed that concomitant meniscal injury increased the risk of early degenerative changes (Chapter 7) and development of knee OA (Chapter 2).

Our findings in the KNALL study regarding the influence of presence of both medial and lateral meniscal injuries and the progression of cartilage defects confirm

the thoughts that the menisci play an important role in reducing contact stresses and friction within the knee joint. For meniscectomy we found in our prospective two-year follow-up study no relationship with early degenerative changes, in contrast to previous reviews which showed that meniscectomy was related with development of knee OA.[24,25] An explanation might be that in the KNALL study exposure of meniscal resection during a period of minimal one and maximal two years was too short for development of early degenerative changes or that morphological changes were not seen with conventional MRI acquisition.

A notable finding in Chapter 2 is the fact that moderate evidence was found for a positive relationship between medial meniscal injury and/ or meniscectomy and development of knee OA. In contrast, based on the findings in the same chapter it seemed that lateral meniscal injury and/ or meniscectomy is not associated with OA development. An explanation might be that the studies had insufficient power; of the 8 studies which evaluated this relationship only three studies had more than 100 patients included in the analysis. Four studies reported the absolute numbers of medial and lateral injury/ meniscectomy: in 3 studies the lateral meniscus was less affected. Anatomically the medial meniscus is more rigid with less anterior posterior mobility than the more mobile lateral meniscus and thus at greater risk for injury.[26] Besides, the medial meniscus is an important stabilizer for anterior-posterior translation in the ACL-deficient knee.[21] It has been shown that during anterior tibial load the forces in the medial meniscus increased in the ACL-deficient knee.[27] Combination of ACL deficiency and medial meniscal injury or resection could influence the increased load on the medial meniscus and thus have an effect on the secondary degenerative changes in the knee. In contrast, the lateral meniscus seems to play a role in the rotational stability during the pivot shift manoeuvre.[21] Thus, lateral meniscal injury or resection in the ACL deficient knee could also increase the load on the underlying cartilage and influence the secondary degenerative changes in the knee. However, in general, medial OA is more common than lateral OA.[28] Greater weight bearing of the medial compartment caused by risk factors as varus malalignment and obesity compared to the lateral compartment might cause this finding.[29] Furthermore, it could be that in addition to the risk factor meniscal injury, other risk factors are needed for development of OA. This is supported by the finding that OA development after meniscectomy is associated with presence of hand OA.[30] Presence of hand OA can be considered as an endogenous risk factor because of its heritability.[31]

Importantly, in the KNALL study both medial and lateral meniscal injuries were related with early degenerative changes in the ipsilateral compartment. Thus, medial meniscal injury was not related with degenerative changes in the lateral compartment and vice versa. Longer follow-up of the KNALL study must investigate the difference

between medial and lateral meniscal injury and meniscectomy after ACL rupture and the relationship with OA development in the medial and lateral compartment.

Cartilage injury

In the KNALL study we found that concomitant medial cartilage defect increased the risk of early degenerative changes after two years. This association was not found for lateral cartilage defects because the prior chance for progression of lateral cartilage defects was already 27% and presence of a cartilage defect laterally at baseline caused an increase of risk of only 2%, namely to 29%. The finding that degenerative changes were especially seen as progression of cartilage defects in the lateral tibiofemoral compartment is in accordance to other studies, which showed that degenerative changes in the lateral compartment were more common in post-traumatic cohorts than in non-traumatic cohorts.[32-34]

Histologic and quantitative MRI studies showed damage of the cartilage composition after the initial ACL trauma up to one year following trauma.[35,36] A dGEMRIC study showed on average of 3 weeks post ACL trauma loss of glycosaminoglycan (GAG) content in both lateral and medial femur, which was positively correlated with synovial fluid GAG content.[37] GAG loss means depletion of proteoglycans, a component of the extracellular matrix of the articular cartilage and is represented as reduced T1 relaxation time during dGEMRIC measurement. The dGEMRIC study showed at an average of 2-year follow-up post ACL trauma that the relaxation time medially did not change between the two MRI assessments but laterally the relaxation time increased, this means restoration of the GAG content and suggesting healing capacity laterally.[38] Recently, Klocke et al imaged ACL patients shortly after ACL rupture with different quantitative MRI methods and their findings suggest that the ACL trauma may cause an influx of water into cartilage but causes no loss of GAG.[39] This is in accordance with the findings of cartilage thickening in the medial part of the femur 2 years after ACL rupture in the study of Frobell et al.[11] Similarly, knees with early radiographic OA had significantly thicker cartilage, especially in the external medial and lateral femur subregions than contralateral knees without osteophytes.[40] Cartilage swelling due to collagen loss and increased permeability of the matrix to water after ACL trauma might be the early phase of biochemical changes of the cartilage resulting in degenerative changes.

With semi-quantitative scoring we found in 3 patients with chronic ACL deficient knees 5 years post ACL trauma cartilage improvement, i.e. cartilage thickening, in the central part of the lateral femur (Chapter 6). Two years after ACL trauma cartilage improvement was present in 6 patients (medial tibiofemoral n=3, lateral tibiofemoral n=3) (not reported data). After careful examination of the baseline and follow-up MRI images the possibility of different slice selection and partial volume averaging was supposed inapplicable.

The found differences between medial and lateral cartilage defects and association with degenerative changes after two-year follow-up or healing capability should be further studied.

Bone marrow lesions

Posttraumatic bone marrow lesions seem to have a healing response, but may influence the subchondral and articular cartilage homeostasis.[35,41-44] This is confirmed by our findings that one year after ACL rupture BMLs in the medial tibiofemoral compartment were associated with ipsilateral cartilage progression (Chapter 7). For the BMLs in the lateral tibiofemoral compartment we could not find this association. As well as previously described, there was no relationship between lateral cartilage defects and ipsilateral cartilage progression. Despite both concomitant lesions were laterally more common than medially at baseline, which is logical because of the specific trauma mechanism of ACL rupture.

Bone mineral density

Interestingly, bone mineral density (BMD) was in the injured knee lower than in the contralateral knee shortly after ACL trauma and during 2-year follow-up. This counted for all regions in the knee: medial, central and lateral tibia and femur. BMD in the operatively treated patients decreased in the first follow-up year and increased in the second follow-up year. An explanation might be the inactivity and change of loading of the knee following ACL rupture and reconstruction. (Chapter 5) Mid- and long-term follow-up should investigate if the BMD in this population will normalize or increase, because animal and clinical studies suggest a biphasic process of BMD changes in OA: a reduction in BMD in the early phase of OA followed by an increase during more advanced phases.[45-52] So, the found lower BMD in the injured knee compared to the healthy knee during the first 2 years after ACL trauma could represent the early phase of OA.

Inflammation-related factors

Cartilage and bone biomarkers and pro-inflammatory cytokines induced after acute knee trauma may play a role in the initiation of the OA process.[53] A recently published study showed that in acutely injured knees with haemarthros and concomitant osteochondral fractures, disrupted cortical bone was related to a higher degree of inflammation in the knee joint.[54] This indicates that the severity of the trauma influences the degree of inflammation. In a case-control study measurement of serum biomarkers pre-injury did not show a difference between ACL-injured patients and matched-controls; however, after ACL rupture a disturbance in cartilage homeostasis was seen.[55] Unfortunately, we have no synovial fluid samples of the patients in the KNALL study,

so we could not investigate the relationship between the inflammatory response in the knee after trauma and development of early degenerative changes. However, blood- and urine samples of the patients, which were collected at baseline, one- and two-year follow-up, should be analysed for the value of biochemical markers. Analysing of these samples can be combined with long-term follow-up of this cohort, so that relationship with OA development can be determined. Disadvantage of serum and urine biomarkers are the lack of specificity for a particular joint and, so far, the biomarkers do not discriminate sufficiently to have diagnostic or prognostic value in the individual patient or to function as outcome measure in clinical trials.[56,57] Furthermore, many biological biomarkers have been identified for studying progression of OA, but few for studying the early stage of OA.[57]

Treatment choice and knee stability

Choice of treatment, i.e. non-operative or operative, did not increase the risk of early degenerative changes (Chapter 7). Moreover, conflicting evidence was found in the literature concerning the relationship with OA development at mid- and long-term follow-up. (Chapter 2) Mechanical knee stability measured by KT 1000 arthrometer and pivot shift test is better in operatively treated patients than non-operatively treated patients.[58,59] However, patient reported outcomes, meniscal lesions and presence of radiographic OA did not differ between the two treatment groups at 5- and 10- year follow-up.[58,59] In Chapter 4 we showed that the ACL in non-operatively treated patients recovered partially concerning ACL features on MRI and measured laxity after two-year follow-up. Follow-up of observational studies suggested that ACL reconstruction is protective against additional injuries, such as subsequent meniscal and chondral lesions.[60,61] However, after summarizing the literature we found moderate evidence for no relationship and conflicting evidence for the relationship between OA development and timing of surgery. (Chapter 2) So, to date the literature is inconclusive whether ACL reconstruction prevents or reduces degenerative changes. An interesting question remains why ACL reconstruction does not prevent degenerative changes. There are several hypotheses. First, ACL reconstruction fails to restore the natural tibiofemoral kinematics in the knee despite of decreased anterior-posterior translation. Persistent tibial subluxation may contribute to OA changes in the knee.[62,63] However, we found that giving way complaints during the first year after ACL rupture were not associated with early degenerative changes. (Chapter 7) It might be that the subluxation moments were not experienced as giving way complaints. Secondly, the degenerative process could be already initiated at the time of injury influenced by other determinants as described previous. Finally, ACL reconstruction causes a new trauma with additional damage such as bone marrow lesions, haemarthros and inflammation-related factors.

So, the optimal treatment option, non-operatively or operatively, for each patient concerning OA development should be further studied. We await with interest the long-term follow-up of the KANON trial[59]. Furthermore, we are conducting a similar study: the COMPARE study (NTR2746), a randomized controlled trial comparing the strategies of non-operative treatment with optional delayed ACL-reconstruction and early operative treatment in patients with an acute ACL rupture. Besides the outcome measures of clinical effect and cost-effectiveness, it is interesting to follow this cohort for the assessment of early, mid- and long-term degenerative changes. Randomized controlled trials are preferred, because in observational studies the intervention might be influenced by confounders as activity level, complaints of the patient and preference for treatment option of the patient and/or orthopaedic surgeon.

LIMITATIONS OF THE STUDY

Prospectively evaluating patients after an acute ACL rupture is valuable in the research field of OA. However, the KNALL study has some limitations. Firstly, the exposure time of some determinants might be too short, e.g. meniscal resection and ACL reconstruction, for finding a relationship with early degenerative changes. The length of two-year follow-up should be prolonged. Secondly, early degenerative changes were only assessed using conventional MRI's, so we have no information of changes in the biochemical composition of cartilage or menisci. Furthermore, some patients underwent already a MRI scan before assessment of eligibility for the study, resulting in the use of different MRI scanners varying from 1.0 to 3.0 Tesla. At follow-up all patients were scanned at a 1.5 Tesla MRI scanner. Thirdly, patients were included in the study between ACL trauma and the first 6 months after trauma. This range of 6 months is large and may cause great variability at baseline measurements. Furthermore, some determinants were assessed subjectively. The Tegner activity score was an indirect measurement of the load of the knee pre- and post ACL rupture. Distinction of load between injured and contralateral knee was not possible. Studying the relationship between changes in load after ACL rupture and early degenerative changes in both operatively and non-operatively treated patients may contribute to increase our knowledge for modifying risk factors. Finally, despite of our sample size of 154 included patients, the power for assessment of relationship between determinants and progressions of early degenerative changes is low, due the low percentage of patients with progression of degenerative changes.

RECOMMENDATIONS FOR FURTHER RESEARCH

Some recommendations for further research have already been described in the previous paragraphs.

In this thesis we aimed to recognize the ACL-patient who will develop OA in the future and which risk factors were present. For influencing the process of early degenerative changes resulting in prevention or postpone OA development, it might be possible to intervene at tissue level or to influence external factors. Treatment targets at tissue level are popular research issues, but very expensive. More applicable treatment options should also receive attention.

The following four main findings concerning risk factors for early degenerative changes were found, concomitant meniscal injury and cartilage defect, presence of BMLs and effusion one year after ACL rupture. Of course, prevention of these factors is the first step. Subsequently, if these factors are present, it is important to know how to treat.

Firstly, this thesis demonstrated that meniscectomy increases the risk for development of degenerative changes, as well as presence of meniscal injury. Does meniscus repair protect against degenerative changes? There is limited evidence that meniscal repair has better radiographic outcome at the long-term compared to meniscectomy. However, partial meniscectomy has a lower reoperation rate than meniscal repair, but meniscal repair with concomitant anterior cruciate ligament reconstruction has a lower reoperation rate compared to isolated meniscal repair.[64] Randomized controlled trials comparing meniscal repair and meniscectomy and the development of degenerative changes are lacking. Furthermore, not all meniscal lesions are suitable for suturing.

Secondly, an important question is: should we treat concomitant cartilage defects directly after ACL rupture? Development of new treatment strategies for preservation of cartilage structure and function is aimed at promoting cartilage repair (growth factors) and catabolic (matrix metalloproteinase inhibitors, aggrecanase inhibitors) pathway enzymes that are dysregulated in OA cartilage.[65] Another strategy is the application of stem cell therapy in repair of cartilage defects. In vitro and animal studies showed promising results, however, for the translation into humans more clinical trials are needed.[66] Furthermore, this treatment option is very expensive. However, all these treatment options are at tissue level; it is more applicable to focus on mechanical prevention of progression of the defects. Advise of avoiding extreme load on the knee or strengthening of the surrounded muscles might contribute to delay or prevent degenerative changes. To date, such studies are lacking, probably due to the limitations of compliance and long-term follow-up. Therefore, development of early degenerative changes could be used as intermediate outcome measure for assessment of the effectiveness of such studies. Another option in patients with ACL rupture and concomitant

cartilage defect could be an osteotomy, if malalignment is present, to decrease the load in the compartment in which the cartilage defect is present.

Thirdly, changes in (subchondral) bone might play a role in development and progression of OA and interact with cartilage degeneration.[67-70] Furthermore, the relationship between traumatic related BMLs and changes in bone mineral density should be further studied for targets to influence bone remodelling.

Finally, effusion could be an indirect effect of inflammation of synovium. Inflammation may play a role in initiating degenerative changes[53,71] and it is suggested that anti-inflammatory therapeutics could play a protective role in cartilage integrity and bone remodelling.[65] The influence of inflammatory responses in post-traumatic OA development should be further studied for developing specific therapeutics.

Mid- and long-term follow-up of the KNALL population is necessary to evaluate the process of degenerative changes. Furthermore, follow-up of this cohort should reveal whether the degenerative changes mainly arise laterally, as shown after two-years in this cohort and in accordance with other studies, where posttraumatic degenerative changes were most common laterally.[32,33] In addition, it will be interesting to see whether the found difference between medial and lateral meniscal injury/ meniscectomy and their relationship with OA development in literature (Chapter 2) also occurs in the KNALL population.

In this thesis we showed that semi-quantitative MRI analyses could identify early degenerative changes for each tissue and that association with risk factors could be identified. It is essential to reach consensus about which semi-quantitative MRI scoring systems should be used for identification of degenerative changes and longitudinal follow-up because of the possibility to compare and/ or pool data of different cohorts. Furthermore, for development of new therapeutics targeting in the early process of OA, it is important to visualize the changes of the composition of cartilage and other tissues, besides the morphologic changes. New MRI techniques measuring cartilage composition are promising research modalities for better understanding of the process of early degenerative changes.[72] Furthermore, as mentioned before, assessment of early degenerative changes can be used as intermediate outcome for evaluating the effect of interventions after ACL rupture resulting in shorter follow-up of longitudinal studies.

An interesting issue, but outside the scope of this thesis is the identification of risk factors and prevention of ACL rupture[73-76] and thus prevention of early development of OA. Neuromuscular training programs may prevent ACL injuries in female athletes.[73,76,77] Future research should investigate the effect of implementation of these prevention programs on a large scale.

For the future it is interesting to compare the results of our study with other post ACL trauma cohorts, such as the KANON study, a randomized controlled trial comparing ACL reconstruction and non-operative treatment of acute ACL injuries in a previously un-injured knee with 2-year and 5-year follow-up.[59,78] Validating each other's results or combining the individual data to increase power would add value for this research issue.

In conclusion, future clinical research and longer follow-up of existing cohorts should focus which ACL patients are at risk for OA development and which modifiable factors can be influenced.

CLINICAL IMPLICATIONS

This thesis shows that early degenerative changes assessed as progression of cartilage defects and osteophytes on conventional MRIs are present two years after ACL rupture. Concomitant meniscal injuries and cartilage defects at time of trauma increase the risk of early degenerative changes, as well as sustained effusion and bone marrow lesion one year after ACL trauma. This knowledge can be used to adapt the rehabilitation if these determinants are present and to inform the patient about the risk of development of OA. Importantly, the choice of treatment, non-operatively or operatively, appears neither to be related to early degenerative changes nor to OA development at the long-term, although based on observational studies.

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Summary

Osteoarthritis (OA) is a common disease of the musculoskeletal system. Prevalence of OA increases; caused by aging of the population and rising prevalence of obesity. OA can arise in all synovial joints, but the knee is most affected. The symptoms (pain, stiffness, decreased joint function) limit daily activities of the patients and negatively influence quality of life. Conservative treatment options, such as exercise, weight reduction in overweight or obese patients, anti-inflammatory drugs and intra-articular injections are mainly aimed at symptomatic relief. If relief of symptoms fails after conservative treatment; osteotomy, unicompartmental arthroplasty and, for end-stage disease, total knee arthroplasty could be considered. Up to now no disease modifying OA drugs has proven to be effective. Knee OA is a multifactorial disease. Well-known risk factors are obesity, female sex, older age and previous knee injury.

Anterior cruciate ligament (ACL) rupture is a common sport related injury, with an annual incidence of approximately 5 to 8 per 10,000 persons in the general population. In athletes the incidence is much higher. Isolated ACL rupture is uncommon, associated injuries accompany at least 50% of the time, such as bone marrow lesions, chondral and meniscal injuries. The impact of an ACL injury is enormous at the short- and mid-term because of a long rehabilitation period and negative influence on knee related quality of live. Besides, these patients have an increased risk for development of knee OA with reported prevalence between 10-90% at 10-20 years post-injury. Because ACL injury is common in the young and active population, these patients will develop OA at a young age. Especially in the young patient with OA the burden will be high because of the long-lasting medical consumption and influence on employment. It would be important to have possibilities to intervene early in the degenerative process and to prevent or postpone total knee arthroplasty. However, not all patients will develop OA after an ACL rupture. Therefore, it is important to identify those patients at risk for degenerative changes.

In this thesis, 'Identification of early degenerative changes in the knee after anterior cruciate ligament rupture', several aspects of the process of ACL rupture leading to OA were studied.

We designed and conducted a prospective observational follow-up study: KNee osteoArthritis anterior cruciate Ligament Lesion (KNALL) study. Early changes after an ACL injury were studied prospectively in both operatively and non-operatively treated patients.

Patients, aged between 18 and 45 years were included within 6 months after initial ACL rupture, diagnosed by physical examination and MRI. Patients with previous knee injury or surgery of involved knee; those with disabling co-morbidity and those with

already osteoarthritic changes on knee radiograph (Kellgren & Lawrence grade >0) were excluded. Measurements were performed at baseline, after one- and two-year follow-up. In total, 154 eligible patients were included.

In **Chapter 2** we systematically reviewed the evidence for determinants of OA in ACL patients. We searched the MEDLINE, Embase, Web of Science and CINAHL databases up to 20th December 2013. Additionally, two reviewers manually and independently screened reference lists of eligible studies. In total 2348 studies were assessed for the following inclusion criteria: randomized controlled trial, prospective study, matched case-control study or retrospective study design with ≥ 20 patients; ACL patients treated operatively or non-operatively; reporting OA as outcome (clinical OA, radiographic OA, OA findings on MRI or during arthroscopy); description of relationship between OA outcome and determinants; determinant must be measured prior to OA outcome; and a follow-up period ≥ 2 years. Of the included studies we independently extracted data and assessed the risk of bias. It was not possible to pool the data for statistical analysis, because the studies were considered clinically heterogeneous with regard to the outcome measures and determinants studied, and therefore we performed "a best-evidence synthesis". Sixty-four publications were included, however, two studies were classified as low-risk of bias. Moderate evidence was the highest level of evidence that was found for associations between determinants and OA development. The included studies showed that medial meniscal injury/ meniscectomy after ACL rupture increases the risk at OA development. In contrast, it seems that lateral meniscal injury/ meniscectomy has no relationship with OA development. Our results suggest that time between injury and surgery does not influence OA development. For many determinants we found conflicting or limited evidence. More low-risk of bias studies are necessary to be able to evaluate the influences of determinants on development of OA after ACL injury.

Chapter 3 was a validation study to evaluate which questionnaire, the Knee Injury and Osteoarthritis Outcome Score (KOOS) or the International Knee Documentation Committee Subjective Knee Form (IKDC subjective), is most useful to evaluate patients with recent ACL ruptures or those within one year of an ACL reconstruction. Both questionnaires are used interchangeably worldwide to monitor ACL patients, however, there is a need for uniformity during the follow-up of these patients. We hypothesized that the IKDC subjective is most useful to evaluate short-term consequences of an ACL rupture. Patients with recent (0-6 months) ACL rupture or those with indications for ACL reconstruction were included. All patients completed the questionnaires shortly after trauma or pre-operatively and again one year later. The KOOS has 5 subscales, each scored separately. The IKDC subjective consists of one total score. The following mea-

surement properties of the KOOS and IKDC subjective were assessed: content validity, construct validity, test-retest reliability, and responsiveness. Regarding content validity, two KOOS subscales (Pain and Activities of Daily Living) were scored as nonrelevant. Two of the 18 questions on the IKDC subjective were assessed as nonrelevant. Only the KOOS subscale Sport and Recreation Function had acceptable construct validity (79% confirmation of the predefined hypotheses). None of the KOOS subscales had a sufficient score for responsiveness (<75% confirmation of the predefined hypotheses). The IKDC subjective scored acceptable for construct validity (84% confirmation of the predefined hypotheses) and responsiveness (81% confirmation of the predefined hypotheses). All KOOS subscales and the IKDC subjective had a reliability (intraclass correlation coefficient [ICC]) of 0.81 or higher. We concluded that the IKDC subjective is more useful than the KOOS questionnaire to evaluate both patients with recent ACL ruptures and those in the first year after ACL reconstruction.

Chapter 4 describes whether ACL features on MRI are improved in patients two years after ACL rupture treated non-operatively, and whether knee laxity, as assessed by physical examination, is improved. Secondly, the relationship between these two diagnostic modalities was analysed. Laxity tests and MRI were performed at baseline and two-year follow-up. Fifty of 143 patients, for whom MRI data at baseline and two-year follow-up were available, were treated non-operatively and were included for this study. Nine ACL features were scored using MRI: fiber continuity, signal intensity, slope of ACL with respect to the Blumensaat line, distance between the Blumensaat line and ACL, tension, thickness, clear boundaries, assessment original insertions and assessment intercondylar notch. A total score was determined by summing scores for each feature. Fiber continuity improved in 30 patients (60%) and the empty intercondylar notch resolved for 22 patients (44%). Improvement in other ACL features ranged from 4-28%. Sixteen patients (32%) improved on the Lachman test (change from soft to firm end points [n=14]; decreased anterior translation [n=2]), one patient (2%) showed improvement with the KT-1000 arthrometer and four patients (8%) improved on the pivot shift test. Improvement on the Lachman test was moderately negatively associated with total score of ACL features at follow-up. Analysing ACL features separately showed that only signal intensity improvement, clear boundaries and intercondylar notch assessment were positively associated with improvement on the Lachman test. The other ACL features were not related with improvement on the Lachman test. This study shows that **t**wo years after ACL rupture and non-operative management, patients experienced partial recovery on MRI and some knee laxity improvement. Improvement of ACL features on MRI correlates moderately with improved laxity.

To improve the knowledge of the process of ACL rupture leading to knee OA, we measured bone mineral density (BMD) in ACL patients, because it seems that bone loss occurs after ACL rupture. The purpose of the study described in **Chapter 5** was to determine BMD changes in the knee after ACL rupture during two-year follow-up period and to compare BMD changes between the injured and healthy contralateral knee. Of 141 patients of the KNALL study at baseline and at the one- and two-year follow-ups, BMD was measured in six regions of the tibia and femur for both knees (medial, central, lateral) using a Dual-energy X-ray Absorptiometry (DXA) scanner. After one year, BMD was significantly lower in all regions of the injured knee of the operatively treated patients compared to baseline. After two years, BMD was significantly increased, but remained lower than the baseline levels. In all regions for all measurements, the mean BMD was significantly lower in the injured knee than in the healthy contralateral knee. We concluded that during a two-year follow-up period after ACL rupture, the BMD level in the injured knee was found to be lower than in the healthy contralateral knee. In operatively treated patients, the BMD decreased in the first year and increased in the second follow-up year.

OA is regarded as a disease of the whole joint with involvement of all tissues. Hence, MRI has become an important tool for OA research because of its capability to visualize all structures in the knee joint. For assessing OA features we used the MRI Osteo-Arthritis Knee Score (MOAKS), a semi-quantitative method, which allows the multi-tissue assessment of OA features in the knee with use of conventional MRI methods. In **Chapter 6** we determined which OA features are detectable in ACL-deficient knees, assessed by MOAKS, and how these features progress during a five-year follow-up. We chose chronic ACL-deficient patients to ensure that development of possible degenerative features was not influenced by surgical procedures. Patients who had a complete ACL rupture five years prior, confirmed by physical examination and MRI within six months of trauma, were eligible for inclusion. Inclusion criteria were no surgical intervention for both knees to date, age at trauma ≤ 45 years, and no clinical signs of OA at the time of trauma. All MRI scans were evaluated according to MOAKS. Thirty patients were included. At follow-up, 7 patients showed progression of cartilage defects in the patellofemoral compartment, 5 in the medial tibiofemoral compartment, and 4 in the lateral tibiofemoral compartment. Four patients had progression of osteophytes in the patellofemoral compartment, 8 in the medial tibiofemoral compartment, and 3 in the lateral tibiofemoral compartment. Medial meniscus pathology progression was scored in 6 patients, and of the lateral meniscus in 7 patients. At follow-up, 2 patients (6.7%) met the MRI-based definition of patellofemoral OA and 7 patients (23.3%) of tibiofemoral OA. It was concluded that MOAKS could detect degenerative changes in chronic ACL-deficient patients. Progression of cartilage, osteophytes, or meniscus

pathology, as assessed with MOAKS, occurred in 70% of patients who were treated non-operatively five years after ACL rupture.

Chapter 7 describes early degenerative changes as assessed on MRI after two years of follow-up in patients with a recent ACL rupture and which determinants are related to these changes. Hundred forty-three patients of the KNALL study completed the two-year follow-up. Patients were treated operatively or non-operatively. MRI scans were evaluated according to the description of MRI Osteoarthritis Knee Score (MOAKS). Early degenerative changes were defined as progression of cartilage defects and osteophytes in tibiofemoral and patellofemoral compartments. Patient characteristics, activity-level, functional instability, treatment and trauma related variables were evaluated as determinants. Early degenerative changes were seen especially as a progression of cartilage defects in the lateral tibiofemoral compartment. In total, progression of cartilage defects and/ or osteophytes in any compartment were present in 40% of the patients. The following determinants were positively significantly associated with early degenerative changes: male gender, cartilage defect in medial tibiofemoral compartment at baseline, presence of meniscal tears, presence of bone marrow lesions in medial tibiofemoral compartment one year after trauma and presence of joint effusion one year after trauma.

Finally, in **Chapter 8** the main findings of this thesis are described and discussed. Also, the limitations of the study and potential for future research are evaluated. Our data showed that early degenerative changes as assessed as progression of cartilage defects and osteophytes on MRI and their related risk factors were identified two years after ACL rupture. Follow-up of the KNALL cohort should reveal whether the degenerative changes mainly arise laterally, as after two-years in this cohort and in accordance with other studies, where posttraumatic degenerative changes were most common laterally. It is important to validate our results with other post ACL trauma cohorts or combine the individual data to increase power. In clinical trials assessment of early degenerative changes can be used as intermediate outcome for evaluating the effect of interventions after ACL rupture resulting in shorter follow-up of longitudinal studies. To date, we have no interventions in clinical practice for influencing the founded risk factors to prevent early degenerative changes. However, the patient should be informed about these risk factors and the long-term consequences.

Nederlandse samenvatting

Artrose is een veel voorkomende ziekte van het bewegingsapparaat. De prevalentie van artrose neemt toe door de vergrijzing van de bevolking en door toename van obesitas onder de bevolking. Artrose kan in alle synoviale gewrichten ontstaan, de knie is echter het meest aangedaan. De symptomen (pijn, stijfheid, verminderde gewrichtsfunctie) beperken de dagelijkse activiteiten van de patiënt en hebben een negatieve invloed op de kwaliteit van leven. Conservatieve behandeling, zoals oefeningen, interventies voor afvallen bij overgewicht en obesitas, anti-inflammatoire pijnmedicatie en intra-articulaire injecties zijn vooral gericht op symptoombestrijding. Indien deze behandelopties falen, kan een standscorrectie van het been, unicompartimentale prothese en voor het eindstadium van artrose, een totale knieprothese overwogen worden. Tot op heden zijn er geen ziekte modificeerbare interventies beschikbaar voor artrose. Knieartrose is een multifactoriële ziekte. Bekende risicofactoren zijn: obesitas, vrouwelijk geslacht, oudere leeftijd en een in het verleden doorgemaakt knieletsel.

Voorste kruisband (VKB) ruptuur is een veel voorkomende sportgerelateerde blessure met een jaarlijkse incidentie van ongeveer 5 tot 8 per 10 000 personen in de algemene populatie. In atleten is de incidentie veel hoger. Bij tenminste 50% van de VKB letsels is er sprake van begeleidend letsel zoals botoedeem, kraakbeen- of meniscusletsel. Een VKB ruptuur heeft een enorme impact voor de patiënt op de korte en middellange termijn vanwege het revalidatieproces en de negatieve invloed op de knie-gerelateerde kwaliteit van leven. Tevens hebben de patiënten na een VKB ruptuur een verhoogde kans op knieartrose. De gerapporteerde prevalenties variëren tussen de 10 en 90% 10 tot 20 jaar na het VKB trauma. Aangezien een VKB ruptuur vooral voorkomt in de jonge en actieve populatie, zullen deze patiënten op relatieve jonge leeftijd knieartrose ontwikkelen. Vooral in de jonge patiënt met knieartrose zullen de gevolgen groot zijn gezien de langdurige medische consumptie en mogelijke invloed op de beroepsuitoefening. Het is van belang vroeg in het degeneratieve proces te kunnen interveniëren en op deze wijze een totale knieprothese (eindstadium van artrose) te voorkomen dan wel uit te stellen. Echter, niet alle patiënten ontwikkelen knieartrose na een VKB ruptuur. Het is daarom belangrijk om de patiënten die na een VKB ruptuur een verhoogd risico hebben op ontwikkeling van degeneratieve veranderingen, te kunnen identificeren.

In dit proefschrift 'Identificatie van vroege degeneratieve veranderingen in de knie na een voorste kruisband ruptuur' werden verschillende aspecten van het proces van VKB ruptuur tot artrose bestudeerd.

Hiervoor werd een prospectieve observationele follow-up studie opgezet, genaamd de KNALL (KNee osteoAthritis anterior cruciate Ligament Lesion) studie. In zowel operatief als conservatief behandelde patiënten werden vroege veranderingen na een

VKB ruptuur prospectief bestudeerd. Patiënten met een leeftijd tussen 18 en 45 jaar, bij wie een VKB ruptuur werd gediagnosticeerd bij lichamelijk onderzoek en bevestigd op MRI, en bij wie het initiële trauma korter dan 6 maanden geleden was opgetreden, werden geïncludeerd. Bij aanwezigheid van de volgende criteria werden patiënten geëxcludeerd: in de voorgeschiedenis een knieletsel of operatie, aanwezigheid van invaliderende comorbiditeit en artrotische veranderingen op de röntgenfoto van de knie (Kellgren & Lawrence graad >0). De metingen werden verricht op baseline, na één en twee jaar follow-up. In totaal werden 154 patiënten geïncludeerd.

In **hoofdstuk 2** hebben we een systematisch overzicht gegeven van de literatuur betreffende determinanten van artrose in patiënten met een voorste kruisband ruptuur. De MEDLINE, Embase, Web of Science en CINAHL databases werden doorzocht. Vervolgens hebben twee beoordelaars onafhankelijk van elkaar de referentie lijsten van de geschikte studies gescreend. In totaal werden 2348 studies gescreend aan de hand van de volgende inclusie criteria: studie-opzet (randomized controlled trial, prospectieve studie, match case-control studie of retrospectieve studie) van minimaal 20 patiënten, VKB patiënten die conservatief of operatief zijn behandeld, artrose als gerapporteerde uitkomstmaat (klinische artrose, radiografische artrose, artrose bevindingen op MRI of tijdens arthroscopie), beschrijving van de relatie tussen de uitkomstmaat artrose en determinanten, de determinant moet gemeten zijn voor de meting van de uitkomstmaat artrose en een minimale follow-up periode van twee jaar. Van de geïncludeerde studies werden de data geëxtraheerd en de methodologische kwaliteit werd door twee beoordeelaars onafhankelijk van elkaar beoordeeld. Er werd een 'best-evidence synthese' verricht omdat het niet mogelijk was om de data van alle geïncludeerde studies samen te voegen voor statistische analyse, vanwege het feit dat de studies te heterogeen waren met betrekking tot de metingen van de uitkomstmaat artrose en de determinanten. Vierenzestig studies werden geïncludeerd, waarvan maar twee studies als 'laag-risico op bias' werden geclassificeerd. Matig bewijs was het hoogste niveau van bewijs dat werd gevonden voor relaties tussen determinanten en artrose ontwikkeling. De geïncludeerde studies toonden aan dat na een VKB ruptuur het risico op artrose toeneemt bij aanwezigheid van mediaal mensicusletsel of meniscectomie. In tegenstelling hiermee lijkt het dat aanwezigheid van lateraal meniscusletsel of verrichtte meniscectomie geen relatie heeft met ontstaan van artrose. De resultaten van dit literatuuronderzoek suggereren dat de tijd tussen VKB trauma en operatie geen invloed heeft op het ontstaan van artrose. Voor veel determinanten vonden we tegenstrijdig of beperkt bewijs. Meer 'laag-risico op bias' studies zijn nodig om de invloed van determinanten op de ontwikkeling van artrose na een VKB ruptuur te evalueren.

In **hoofdstuk 3** is een validatie studie beschreven, waarin wordt geëvalueerd welke vragenlijst, de Knee Injury and Osteoarthritis Outcome Score (KOOS) of de International Knee Documentation Committee Subjective Knee Form (IKDC subjectief) het meest bruikbaar is om patiënten met een recente VKB ruptuur of patiënten in het eerste jaar na een VKB reconstructie te monitoren. Beide vragenlijsten worden wereldwijd door elkaar gebruikt om VKB patiënten tijdens follow-up te monitoren. Er is echter uniformiteit nodig. Onze hypothese was dat de IKDC subjectief meer bruikbaar is om de korte termijn consequenties van een VKB ruptuur te evalueren. Patiënten met een recente (0 – 6 maanden) VKB ruptuur of patiënten met een indicatie voor een VKB reconstructie werden geïncludeerd. Alle patiënten vulden de vragenlijsten kort na het trauma of preoperatief in en na 1 jaar opnieuw. De KOOS heeft 5 subschalen, iedere schaal wordt apart gescoord. De IKDC subjectief bestaat uit één totaal score. De volgende eigenschappen van de KOOS en de IKDC subjectief werden beoordeeld en vergeleken: content validiteit, construct validiteit, test-hertest reproduceerbaarheid en responsiviteit. Twee KOOS subschalen (*Pijn* en *Functioneren in het dagelijkse leven*) werden beoordeeld als niet relevant wat betreft de content validiteit. Bij de beoordeling van de content validiteit van de IKDC subjectief werden twee van de 18 vragen als niet-relevant gescoord. Alleen de KOOS subschaal *Functioneren in vrije tijd en sport* had een acceptabele construct validiteit (79% bevestiging van de vooraf gedefinieerde hypotheses). Geen van de KOOS subschalen had een voldoende score voor de responsiviteit (< 75% bevestiging van de vooraf gedefinieerde hypotheses). De IKDC subjectief had acceptabele scores voor de construct validiteit (84% bevestiging van de vooraf gedefinieerde hypotheses) en responsiviteit (81% bevestiging van de vooraf gedefinieerde hypotheses). Alle KOOS subschalen en de IKDC subjectief hadden een goede score bij de beoordeling van test-hertest reproduceerbaarheid (intraclass correlatie coëfficiënt van 0.81 of hoger). We concludeerden dat de IKDC subjectief beter bruikbaar is dan de KOOS vragenlijst om patiënten met een recente VKB ruptuur en patiënten in het eerste jaar na een VKB reconstructie te monitoren.

Hoofdstuk 4 beschrijft welke VKB kenmerken op MRI veranderen twee jaar na een VKB ruptuur in patiënten die conservatief zijn behandeld. Daarnaast hebben we beoordeeld of de knie laxiteit gemeten bij lichamelijk onderzoek, is veranderd. Tenslotte werd de relatie tussen deze twee diagnostische modaliteiten geanalyseerd. MRI en laxiteitstesten werden verricht op baseline en na twee jaar follow-up. Vijftig van de 143 patiënten, van wie alle MRI data beschikbaar waren, werden conservatief behandeld en geïncludeerd in deze studie. De volgende negen VKB kenmerken werden gescoord op MRI: vezel continuïteit, signaal intensiteit, helling van de VKB in relatie tot de Blumensaat lijn, afstand tussen de Blumensaat lijn en VKB, spanning van de VKB, dikte van de VKB, duidelijke begrenzing van de VKB, beoordeling van aanwezigheid van weefsel buiten

de originele inserties en beoordeling van de intercondylaire notch. De totale score werd bepaald door alle scores van de kenmerken op te tellen. Score 0 betekent dat alle VKB kenmerken als normaal zijn gescoord, hoe hoger de score hoe meer VKB kenmerken als abnormaal zijn gescoord (maximale score is 10). Vezel continuïteit verbeterde in 30 patiënten (60%) en de 'empty intercondylaire notch' verdween in 22 patiënten (44%). Verbetering van de andere VKB kenmerken op MRI varieerden tussen de 4 en 28%. Zestien patiënten (32%) verbeterden op de Lachman test (n = 14: verandering van zacht naar hard eindpunt; n = 2 afname anterieure translatie), één patiënt (2%) toonde verbetering op de KT-1000 arthrometer en 4 patiënten (8%) verbeterden op de pivot shift test. Verbetering op de Lachman test was matig negatief geassocieerd met de totale score van de VKB kenmerken op follow-up, dit betekent dat de waarschijnlijkheid op verbetering van de Lachman test groter is bij een lagere totaal score. Na analyse van de VKB kenmerken afzonderlijk, hadden verbetering van signaal intensiteit, duidelijke begrenzing van de VKB en beoordeling van de intercondylaire notch een positieve associatie met verbetering op de Lachman test, dit betekent dat de waarschijnlijkheid op verbetering op de Lachman test groter is bij verbetering van deze drie VKB kenmerken. De andere VKB kenmerken waren niet gerelateerd aan verbetering op de Lachman test. Deze studie toont aan dat patiënten die conservatief behandeld zijn, twee jaar na een VKB ruptuur gedeeltelijk herstel laten zien op MRI en enige verbetering wat betreft de knie laxiteit. Verbetering van VKB kenmerken op MRI correleert matig met verbeterde laxiteit.

Om de kennis van het proces van VKB ruptuur tot knieartrose te verbeteren, hebben we de botdichtheid van de knie in VKB patiënten gemeten, omdat er aanwijzingen zijn dat er botverlies optreedt na een VKB ruptuur. Het doel van de studie die beschreven wordt in **hoofdstuk 5** was om de botdichtheid veranderingen in de knie na een VKB ruptuur gedurende 2 jaar follow-up te beoordelen en om eventuele botdichtheid veranderingen tussen de aangedane knie en de gezonde contralaterale knie te vergelijken. Op baseline, na één en twee jaar follow-up werd van 141 patiënten uit de KNALL studie de botdichtheid gemeten in 6 regio's van de tibia en femur van beide knieën (mediaal, centraal en lateraal). De metingen werden verricht door een Dual-energy X-ray Absorptiometry (DXA)-scanner. In alle regio's op alle meetmomenten was de gemiddelde botdichtheid significant lager in de aangedane knie vergeleken met de gezonde contralaterale knie. Na één jaar was de botdichtheid significant lager in alle regio's van de aangedane knie van de operatief behandelde patiënten in vergelijking met de baseline meting. Na twee jaar was de botdichtheid significant toegenomen, maar bleef lager dan op baseline. We concludeerden dat gedurende een periode van twee jaar follow-up na een VKB ruptuur de botdichtheid in de aangedane knie lager is in vergelijking met de gezonde

contralaterale knie. In operatief behandelde VKB patiënten nam de botdichtheid in het eerst jaar af en steeg in het tweede follow-up jaar.

Artrose wordt beschouwd als een ziekte van het gehele gewricht waarbij alle structuren zijn betrokken. MRI heeft een belangrijke rol binnen het artrose onderzoek gekregen, aangezien het alle structuren in de knie kan weergeven. Om artrose kenmerken te kunnen beoordelen hebben we gebruik gemaakt van de OsteoArthritis Knee Score (MOAKS), een semi-kwantitatieve scoringsmethode waarmee alle structuren in de knie op artrose kenmerken worden beoordeeld. Deze score kan toegepast worden op conventionele MRI methodes. In **hoofdstuk 6** hebben we onderzocht welke artrose kenmerken, gescoord met de MOAKS, geïdentificeerd kunnen worden in knieën van patiënten met een VKB deficiëntie en hoe het verloop is van deze artrose kenmerken gedurende een periode van 5 jaar follow-up. Er is gekozen voor patiënten met chronische VKB deficiëntie om er zeker van te zijn dat mogelijke ontwikkeling van degeneratieve veranderingen niet beïnvloed is door operaties. Patiënten bij wie 5 jaar geleden een complete VKB ruptuur was gediagnosticeerd bij lichamelijk onderzoek en bevestigd op MRI binnen 6 maanden na het trauma, waren geschikt voor inclusie. Inclusie criteria waren: in het verleden geen operatieve interventies aan beide knieën, leeftijd ten tijde van het trauma ≤ 45 jaar en geen klinische tekenen van artrose ten tijde van het trauma. Alle MRI scans werden beoordeeld volgens de MOAKS. Dertig patiënten werden geïncludeerd. Op follow-up werd bij 7 patiënten progressie van kraakbeendefecten in het patellofemorale compartiment gezien, bij 5 patiënten in het mediale tibiofemorale compartiment en bij 4 patiënten in het laterale tibiofemorale compartiment. Vier patiënten hadden progressie van osteofyten in het patellofemorale compartiment, 8 in het mediale tibiofemorale compartiment en 3 in het laterale tibiofemorale compartiment. Progressie van mediale meniscus pathologie werd bij 6 patiënten waargenomen en voor de laterale meniscus bij 7 patiënten. Na 5 jaar follow-up voldeden 2 patiënten (6.7%) aan de MRI definitie voor patellofemorale artrose en 7 patiënten (23.3%) voor tibiofemorale artrose. Op basis van de resultaten van deze studie werd geconcludeerd dat de MOAKS degeneratieve veranderingen kan identificeren bij patiënten met een chronische VKB deficiëntie. In 70% van de patiënten met een VKB ruptuur die conservatief behandeld zijn, werd 5 jaar na het trauma progressie van kraakbeendefecten, osteofyten of meniscus pathologie geïdentificeerd op MRI.

Hoofdstuk 7 beschrijft welke vroege degeneratieve veranderingen in de knie worden waargenomen op MRI bij patiënten met een recente VKB ruptuur na twee jaar follow-up en welke determinanten gerelateerd zijn aan deze veranderingen. Twee jaar follow-up data was compleet van 143 patiënten van de KNALL studie. Patiënten waren conservatief of operatief behandeld. MRI scans werden beoordeeld volgens de

beschrijving van de MRI Osteoarthritis Knee Score (MOAKS). Vroege degeneratieve veranderingen werden gedefinieerd als progressie van kraakbeendefecten en osteofyten in de tibiofemorale en patellofemorale compartimenten. Patiënt karakteristieken, activiteitenniveau, functionele instabiliteit, behandeling en traumagerelateerde variabelen werden bestudeerd als determinant. Vroege degeneratieve veranderingen werden vooral waargenomen als progressie van kraakbeendefecten in het laterale tibiofemorale compartiment. In totaal werd in 40% van de patiënten progressie van een kraakbeendefect en/ of osteofyt in een compartiment waargenomen. De volgende determinanten hadden een positieve significante relatie met vroege degeneratieve veranderingen: mannelijk geslacht, kraakbeendefect in het mediale tibiofemorale compartiment op baseline, aanwezigheid van een meniscusscheur, aanwezigheid van botoedeem in het mediale tibiofemorale compartiment na één jaar follow-up en effusie in het kniegewricht na één jaar follow-up.

In **hoofdstuk 8** worden de belangrijkste bevindingen van dit proefschrift beschreven en bediscussieerd. Tevens worden de beperkingen van deze studie en mogelijkheden voor toekomstig onderzoek besproken. De resultaten van onze studie hebben aangetoond dat vroege degeneratieve veranderingen, gemeten als progressie van kraakbeendefecten en osteofyten op MRI, en de hieraan gerelateerde risicofactoren werden geïdentificeerd twee jaar na een VKB ruptuur. Uit langere follow-up van het KNALL cohort moet blijken of de degeneratieve veranderingen vooral in het laterale compartiment ontstaan, zoals na twee jaar in dit cohort en zoals in overeenstemming met andere studies waar post-traumatische degeneratieve veranderingen vooral lateraal ontstonden. Het is belangrijk om onze resultaten te valideren met resultaten van andere VKB trauma cohorten of om de data van de verschillende cohorten te combineren zodat de power van de studie wordt vergroot. Beoordeling van vroege degeneratieve veranderingen kan in klinische trials gebruikt worden als intermediaire uitkomst voor evaluatie van het effect van interventies na een VKB ruptuur, waardoor de follow-up in longitudinale studies korter kan zijn. Tot op heden zijn er geen interventies in de klinische praktijk om de gevonden risicofactoren te beïnvloeden ter preventie van degeneratieve veranderingen na een VKB ruptuur. Het is echter wel belangrijk dat de patiënt wordt geïnformeerd over deze risicofactoren en de lange termijn consequenties na een VKB ruptuur.

Dankwoord

DANKWOORD

Dit proefschrift is mede tot stand gekomen door de inspiratie, kennis, hulp, en betrokkenheid van meerdere personen. Graag wil ik iedereen bedanken die direct of indirect een bijdrage heeft geleverd aan dit proefschrift. Tot een aantal mensen wil ik in het bijzonder het woord richten en mijn dank betuigen.

Allereerst wil ik het woord richten tot mijn copromotor, dr. M. Reijman. Beste Max, jouw inbreng en betrokkenheid bij de KNALL studie is onmisbaar geweest. De vele overleg momenten gaven het project steeds weer dat zetje in de goede richting. Tevens zorgde jouw onderzoeks-blik ervoor om verder te kijken dan de mogelijkheden en grenzen van de klinische praktijk. Dit leidde soms tot irreële suggesties, maar door dit hoger streven werd er wel vooruitgang geboekt. Jouw deur stond altijd open voor overleg, het direct bespreken van een bijzonder resultaat en voor dat gezellige praatje waaronder de vele evaluaties en discussies over alle sportactiviteiten van het voorafgaande weekend. Dat heb ik altijd erg gewaardeerd. Jouw betrokkenheid en doorzettingsvermogen bleven niet beperkt tot de wetenschap. Op de Alpe d'Huez werd tot het uiterste gegaan. En na dat afzien op de fiets, was er direct de gezelligheid die onze onderzoeksgroep kent van de etentjes in het Rotterdamse. Kortom, Max, bedankt voor de bijzondere tijd waarin je mijn interesse voor het doen van onderzoek gestimuleerd hebt. Tot slot moet ik zeggen, dat ik blij ben dat de promotie niet op 1 april is, gezien mijn vrees voor wraak op de ontsteltenis die toch even bezit van je nam in een ver verleden op deze dag na het lezen van 'die zeer officiële mededeling' …….

Aan mijn promotor, Prof. dr. S.M.A. Bierma-Zeinstra, ben ik ook veel dank verschuldigd. Beste Sita, van copromotor werd je promotor gedurende mijn onderzoeksproject en hiermee groeide ook jouw agenda, desondanks bleef je toegankelijk. Ik bewonder jouw vermogen om gedurende een overleg moment direct overzicht te hebben en inventieve suggesties te geven voor het onderzoek. Jouw oplossingen en suggesties die altijd dicht tegen de klinische praktijk aan liggen, hebben voor de nodige duidelijkheid en helderheid van dit klinische onderzoek gezorgd.

Mijn tweede copromotor, dr. D.E. Meuffels, wil ik ook graag in het bijzonder noemen. Beste Duncan, ik heb veel respect voor het combineren van al jouw activiteiten binnen de wetenschap en het klinische werk. Jouw inspanning en gedrevenheid die je hebt gelegd in dit project is van grote waarde geweest. Zonder jouw altijd positieve houding ten aanzien van de inclusies waren we niet bij dit aantal gekomen. Het feit dat je altijd bereid was om tussen je werkzaamheden door even jouw visie op een röntgenfoto of MRI te geven, mij deelgenoot te maken van jouw kennis, dan wel iets te bespreken, heb

ik erg op prijs gesteld. Jouw creatieve wetenschappelijke blik en oplossingen voor praktische problemen zijn erg constructief geweest voor dit proefschrift. Ook de gesprekken ten tijde van mijn besluit over de switch van orthopaedie naar sportgeneeskunde heb ik gewaardeerd. Marta, dank voor je Spaanse gastvrijheid. Duncan, ik hoop dat we in de toekomst onze samenwerking zullen voortzetten, zowel in de wetenschap als in de klinische praktijk.

Beste Professor Verhaar, graag wil ik u bedanken dat u mij destijds heeft aangenomen voor dit project en mij hierdoor de kans heeft gegeven om ervaring op te doen binnen de wetenschap. Tevens wil ik u bedanken voor uw suggesties binnen het project en uw kritische blik op de manuscripten.

Een belangrijk onderdeel van een promotietraject zijn je kamergenoten, met wie je serieuze onderzoeksgerelateerde problemen dan wel resultaten moet kunnen bespreken, maar met wie je ook je frustraties kunt relativeren en veel moet kunnen lachen. In het begin van mijn traject was Hs-104 nog klein, maar in de afgelopen jaren is de Hs-104 groep steeds verder uitgebreid.

Maaike, jij bent de 'oudste' van Hs-104. Dank voor de vele tips die je mij hebt gegeven ten tijde van het opzetten van de KNALL studie en ook voor het samenwerken op het wetenschappelijk gebied. Je bent een goed voorbeeld geweest voor mij en dan denk ik met bewondering terug aan jouw georganiseerdheid en punctualiteit. Ik vind het erg leuk dat we, ondanks dat we geen collega's meer zijn, nog steeds contact hebben.

Carin, we zaten in hetzelfde introductieklasje van nieuwe medewerkers van het Erasmus MC, pas op het einde van de dag wisten we dat we collega's werden bij de orthopaedie. Direct vanaf het moment dat je in Hs-104 kwam zorgden jouw humor en gezelligheid voor een erg leuke periode. Zo werd bijvoorbeeld het saaie SPSS bestanden controleren een super gezellige avond. De voor ons ingewikkelde ICT problemen waren voor jou 'een makkie' en werden door jou zonder enige moeite opgelost. Eigenlijk had je op bijna alle openstaande vragen al googelend direct een antwoord. Dank voor je adviezen en vooral voor je vriendschap.

Job, je kwam op de kamer met 3 dames, dat viel je soms wat zwaar, maar gelukkig hebben we vooral veel gelachen en mede door jouw komst, kwamen er de gezellige etentjes. Jouw adviezen over leuke restaurants in Rotterdam of goede recepten heb ik graag ter harte genomen. Heel veel succes met de laatste loodjes voor jouw proefschrift en de keuzes met betrekking tot je vervolg carrière.

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ik vele dingen goed bespreken: van logistieke problemen van de studie, frustraties van mislopende inclusies of niet komende follow-uppers, tot het 'nabespreken' van mijn wedstrijden en het geneuzel over jouw evenbeeld Ronaldo versus Messi . Je bent een oprecht en behulpzaam persoon.

Guus, ik heb veel respect voor het feit hoe jij jouw logistiek ingewikkelde multicenter studie draaiende hebt gehouden met een erg mooie publicatie als resultaat. Naast jouw kwaliteiten als onderzoeker, zorgde jij ook voor gezelligheid en humor in Hs-104. Ik heb altijd alle sportmomenten met en zonder competitie element, zoals het mountainbiken, schaatsen, wielrennen in Limburg en de Alpen en de kwart triatlon in Breukelen erg gewaardeerd. Gelukkig blijven we collega's in hetzelfde vakgebied.

Eline, binnen het klinische onderzoek ben je een onmisbaar persoon. Geweldig hoe jij meerdere studies draaiende houdt. Ook jouw verfrissende kijk op zaken was een meerwaarde voor mijn project. Dank voor alle hulp en feedback. Daarnaast ben jij natuurlijk een belangrijk persoon voor de continuïteit in Hs-104.

Tijs, ik vind het bewonderenswaardig hoe snel jij jouw project hebt opgezet, je artikelen voor het proefschrift tot stand hebt gebracht en in opleiding tot orthopaedisch chirurg bent gekomen. Dat snelle had jij ook tijdens het baantjes trekken in het zwembad. Jouw passie voor Rotterdam en Feyenoord vind ik erg mooi en je bent een leuke collega. Dank voor de gezellige momenten.

Desiree, jouw vele tips over Breda zorgden ervoor dat ik de stad al kende voordat ik er woonde. Ik heb veel respect dat je de keuze hebt gemaakt om naar het noorden te verhuizen voor de opleiding. Heel veel succes in je verdere loopbaan.

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Ook ben ik alle stafleden van de afdeling orthopaedie dankbaar voor de prettige samenwerking. Een speciaal woord van dank wil ik richten aan Rien Heijboer en Gert Bessems. Beste Rien, ik zal nooit de volgende tekst van een profvoetballer vergeten: 'Ik vind dr. Heijboer zo'n aardige en goede dokter en hij is zo gewoon gebleven', nadat je in enkele minuten de wedstrijd van het afgelopen weekend en de andere uitslagen had doorgenomen met de desbetreffende patiënt, en ondertussen de knie had onderzocht en feedback had gegeven op mijn bevindingen en plan. Dank voor alle inclusies en kennisoverdracht. Naast de gesprekken over VKB letsels en andere sport gerelateerde blessures vond ik de gesprekken over de verschillen en overeenkomsten tussen het voetbal en hockey boeiend. Ik hoop dat ik als toekomstig sportarts nog van jouw expertise in de sportorthopaedie kan leren.

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En natuurlijk wil ik alle (oud) arts-assistenten orthopaedie, David, Alexander, Maurik, Tom, Olav, Judith, Suzanne, Wouter, Wahid, Justus, Aernout, Gerald, Hanneke, Margot, Imme, Yvon, Demien, Deniz, Leon, Peter en Paul, bedanken voor hun bijdrage aan de KNALL studie en leuk tijd in het Erasmus MC.

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Beste Simone, dank voor het snel regelen van afspraken en alle andere administratieve zaken en bovenal de voor jouw zo kenmerkende vrolijkheid. Esther, je bent alweer een tijdje weg uit het ziekenhuis. Jouw vriendelijkheid en behulpzaamheid hebben ervoor gezorgd dat ik me als nieuwe arts-onderzoeker direct welkom voelde. Ook wil ik alle medewerkers van de polikliniek bedanken voor hun hulp bij de afspraken van de KNALL patiënten.

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de eerste editie van het congreskrantje gemaakt, dus daar moet zeker een vervolg op komen.

In dit project was een goede samenwerking tussen de orthopaedie en radiologie onontbeerlijk. Beste Edwin, jouw betrokkenheid binnen de KNALL studie is van groot belang geweest. Ik heb veel geleerd van de vele overlegmomenten over de MRI bevindingen. Ook jouw kritische blik op de manuscripten hebben tot een beter eindresultaat geleid.

Aan alle orthopaedisch chirurgen en arts-assistenten orthopaedie van het MC Haaglanden ben ik mijn dank verschuldigd voor alle inclusies. In het bijzonder wil ik een woord tot Ewoud richten. Beste Ewoud, dank voor jouw gedrevenheid om alle VKB patiënten in de KNALL studie te includeren en natuurlijk ook voor jouw snelle klinische blik op iedere KNALLer tijdens een overvol combinatiespreekuur. Ik kijk er naar uit om straks tijdens mijn orthopaedie deelstage veel van jou te leren.

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Zonder de afdeling Sportgeneeskunde van het MC Haaglanden was deze studie niet geslaagd, gezien de vele inclusies van 'verse' kruisband rupturen die werden aangedragen. Cora en de sportartsen, Don, Hans, Adam en destijds arts-assistenten in opleiding Mirjam, Bas, Petra, Floor en Robert-Jan wil ik hartelijk bedanken voor hun bijdrage.

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mijn onnozele Apple vragen. Maar je was vooral een erg goede en loyale teamgenoot. Marianne, Dijkert, ik vond het leuk om samen met jou op het middenveld te spelen. Niet alleen vulden we elkaar goed aan maar er ontstond soms ook de nodige reuring die je opriep met je creativiteit of met oprechte boosheid dan wel rebels gedrag. En natuurlijk dank voor alle moderne media lessen en voor jouw inbreng bij het tot stand komen van de kaft van dit boekje. Mariek, ik denk dat ik met jou de meeste minuten in het veld en in de zaal heb gestaan. Het samenspel in de zaal was genieten. We waren een sterk duo en in de loop der jaren hebben we steeds beter elkaars sterke punten gebruikt. Wat hebben we vele uren ergens in Utrecht bij het scheiden van de fietswegen nog na staan kletsen over de wedstrijd, trainingen of hele andere zaken! Onze liefde voor sport, maakt onze band bijzonder. Ik heb veel respect voor jouw passie en gedrevenheid. Claire, onze kernwoorden: ongelooflijk fantastisch! Dank voor alle mooie momenten en onze vriendschap. Lot, een groot deel van mijn hockeyleven heb ik samen met jou gespeeld. Als speelsters waren we erg verschillend, jij creatief op links met een machtig schot, ik meer defensief in het centrum. En buiten het veld: jij wat excentriek, ik wat behoudend, maar misschien juist daardoor dikke maatjes. Gedurende onze tijd bij Kampong zagen en spraken we elkaar bijna iedere dag. Nu we niet meer samen hockeyen en door alle drukte, is dat een stuk minder geworden, maar als we elkaar spreken is het weer als vanouds.

Ook na het afsluiten van mijn hockeytijd vond ik het heerlijk om het werk af te wisselen met een fanatieke sporttraining. Ik wil dan ook alle trainingsgenoten van de B-selectie van PAC Rotterdam onder de bezielende leiding van Rob en RT3 van Sprint in Breda bedanken voor de verfrissende hardlooptrainingen en in het bijzonder de trein Marloes, Helen, Elles en Amy.

Ludiekers, de afgelopen jaren was ik wat minder aanwezig bij alle gemeenschappelijke activiteiten. Ik waardeer onze vriendschap en de verscheidenheid aan persoonlijkheden binnen onze groep maakt dit bijzonder. Maud, dank voor alle tips met betrekking tot de promotie die jij als 'Belgisch' ervaringsdeskundige hebt gegeven.

Jet, ik wil ook jou bedanken voor je relativeringsvermogen waardoor de zaken dan weer wat simpeler worden en natuurlijk voor de Endnote les.

Dit proefschrift kan natuurlijk niet verdedigd worden zonder de steun en aanwezigheid van mijn paranimfen.

Caro, onze vriendschap begon op de Parkstraat. Eén van *de* momenten op de Parkstraat was toch wel de triomf van dat grote lekkernij pakket, dat ons toegezonden werd na een ware pleitnota van jouw meesterhand over een misvormde M&M. Vele etentjes

volgden, meestal op huislocatie 'De Eik' in Utrecht. Het waren gezellige momenten om even bij te kletsen, het promotiegezeur los te laten of het daar juist over te hebben. Ik ben je dankbaar voor het aanhoren van mijn twijfels en het geven van advies met betrekking tot die moeilijke keuze in het afgelopen jaar. We vonden elkaar ook in het fanatisme voor de sport. Jij vooral als kijker. Bij ieder groot sportevenement troefde je mij volledig af met je kennis over onze favorieten. En natuurlijk super, hoe voortvarend jij en Gert Jan, als een professioneel organisatiebureau, mij al hebben geholpen bij de voorbereidingen rondom de promotie.

Mau, als broer ben je natuurlijk het grote voorbeeld in meerdere opzichten. Deels onbewust doe ik je in heel veel dingen na, zoals onder andere de stap om eerst een promotietraject te starten en dan pas in opleiding te gaan. Het overkomt mij nu zelfs ook al dat ik elke ochtend in één lange sprint naar het station race. Ik heb bewondering voor jouw precisie en het vermogen om de meest briljante teksten te schrijven. Ik weet hoe jij je ergens in vastbijt totdat het is volbracht. Je bent iemand van uitersten en afzien, ook in de sport, leidend en al lijdend tot grote prestaties. Deze eigenschappen zorgden ervoor dat mijn vragen omtrent de inhoud van dit drukwerk altijd zeer nauwkeurig en uitgebreid beeldend werden beantwoord. Hopelijk is jouw eindoordeel 'niet onaardig'. Aan de deadline van de pedel aan de Nieuwe Gracht heb ik me helaas niet gehouden, maar gelukkig staat nu de datum.

Mam en pap, zoals het verhuisbedrijf "de Pin" iedere keer weer klaar stond, ongeacht het tijdstip, vond ik bijzonder en was van grote waarde aangezien de verhuizingen altijd onder de nodige tijdsdruk plaatsvonden. Ook jullie support tijdens het hockeyen vond ik erg leuk.

Pap, dank voor de enorme vele kilometers die je heb gereden voor allerlei soorten vrachten: taxiritjes, verhuisdozen, asperges, fietsen of houtvoorraden. Ook was 's nachts een ritje Rotterdam voor het dichttimmeren van ramen na een inbraak geen enkel probleem. Alle klussen werden in een uiterst snel tempo geklaard. Er was iets bedacht en een week later had je het geregeld, zo ook de kerstkaart die de aanzet heeft gegeven tot de kaft van dit drukwerk. Deze snelheid schoot soms door tijdens het gebruik van je digitale apparatuur met als gevolg zwarte schermen. Jouw altijd positieve kijk op zaken, maakt dat ik de negatieve dingen kan relativeren. Pap, bedankt voor het vele onderhandelen, meestal voor een goede fles wijn, en jouw wijnadviezen.

Mam, ik bewonder jouw multi-talent: van binnenhuis architect, makelaar in vele steden, coach, uitzendbureau, chef kok, dierenverzorgster, hoofdzuster, reisbureau voor bijzondere locaties, bibliothecaresse, neerlandicus, editor tot hardloopster. Jouw speurwerk, volhardendheid en nauwkeurigheid zorgen ervoor dat jij een expert bent of wordt in verschillende vakgebieden. De kennisoverdracht die hierop volgt is altijd zeer uitgebreid en gedetailleerd. Zo hebben wij onder andere buiten de wet tredende

huiseigenaren goed van repliek kunnen voorzien. Dank voor de oplossingsgerichte adviezen en het meedenken over moeilijke beslissingen gedurende de vele lange en ook altijd erg gezellige telefoongesprekken.

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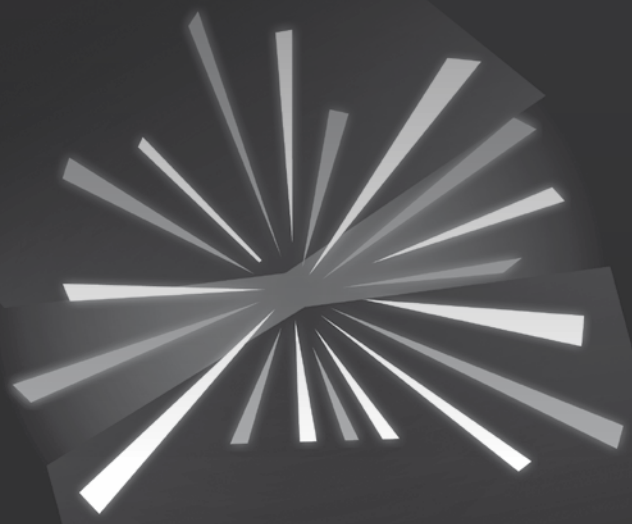
Curriculum vitae

CURRICULUM VITAE

Belle van Meer was born on 18th of March 1982 in Bergen op Zoom. In 2000, after she passed her Gymnasium exam at the Moller Lyceum in Bergen op Zoom, she started her medical education at Utrecht University. Part of her clinical study was carried out in Curaçao (St. Elisabeth Hospital, Willemstad) and Sri-Lanka (Tsunami medical care, Colombo). She combined her interest in sports and medicine during her research internship on overtraining syndrome and head injuries in field hockey at the Department of Sports Medicine at the University Medical Center Utrecht. In 2007 she obtained her medical degree and started to work at the Sports Medical Center of the Royal Dutch Football Association (KNVB). She started in 2008 the research project, which is described in this thesis, at the Department of Orthopaedic Surgery at the Erasmus MC, University Medical Center Rotterdam (dr. M. Reijman, dr. D.E. Meuffels and prof. dr. S.M.A. Bierma-Zeinstra) in collaboration with the Departments of Sports Medicine and Orthopaedic Surgery at Medical Center Haaglanden, The Hague (dr. E.R.A. van Arkel). In 2012 she won the 'Eikelaar' award for the best oral presentation at the annual congress of the Dutch Arthroscopy Society and in 2013 she was awarded for the best oral presentation regarding clinical studies at the annual congress of the Dutch Orthopaedic Association. She started in 2013 as a resident at the Department of General Surgery at St. Elisabeth Hospital in Tilburg (dr. P.W.H.E. Vriens) as part of the residency training program in Orthopaedic Surgery. In 2014 she decided to focus on Sports Medicine. Therefore, to gain experience in Cardiology she worked as a resident at the Department of Cardiology at St. Lucas Andreas Hospital in Amsterdam (dr. J.M. Schroeder-Tanka and dr. A.R. Willems). During her study and work she played field and indoor hockey at elite level. With the Dutch national indoor hockey team she played several European and World Championships. In 2007 she became with her team World Champion in Vienna. In 2011 she was awarded as best player and topscorer of the World Championship indoor hockey tournament in Poznan. As of January 2015 she works as a resident at the department of Cardiology at the Medical Center Haaglanden, The Hague, as part of the residency training program in Sports Medicine under the supervision of cardiologist dr. R.F. Veldkamp and sports medicine physician drs. R.F. van Oosterom.

PhD Portfolio Summary



PHD PORTFOLIO

Name PhD student: B.L. van Meer
Erasmus MC Department: Orthopaedic Surgery

Promotor: Prof. dr. S.M.A. Bierma-Zeinstra
Copromotoren: dr. M. Reijman, dr. D.E. Meuffels
Supervisor: dr. M. Reijman

1. PhD training

	Year	Workload (ECTS)
In-depth courses		
Clinimetrics course	2008	1.0
Methodologie van patiëntgebonden onderzoek en voorbereiding subsidieaanvragen	2009	0.3
Introduction to Data-analysis (NIHES)	2009	1.0
Cohort Studies (NIHES)	2009	0.7
Basiscursus regelgeving en organisatie voor klinische onderzoekers (BROK)	2009	1.0
Clinical Decision Analysis (NIHES)	2010	0.7
Markers and Prognostic Research (NIHES)	2010	0.7
English Biomedical Writing and Communication course	2011	4.0
Regression analysis for Clinicians (NIHES)	2013	1.9
Podium presentations		
KOOS of IKDC? Welke vragenlijst is het geschiktst voor het monitoren van patiënten met een voorste kruisband ruptuur? Sportmedisch Wetenschappelijk Jaarcongres van de Vereniging voor Sportgeneeskunde (VSG), Noordwijkerhout, the Netherlands	2010	1.0
KOOS or IKDC? Which questionnaire is most useful for monitoring patients with an anterior cruciate ligament injury? Annual congress of the Dutch Arthroscopy Society (NVA), Ermelo, the Netherlands	2011	1.0
Determinants influencing development of osteoarthritis after an anterior cruciate ligament injury: a systematic review. Annual congress of the Dutch Arthroscopy Society (NVA), Den Bosch, the Netherlands ***Awarded best oral presentation*: *Eikelaar prijs***	2012	1.0
Is er anatomisch en functioneel herstel na een voorste kruisband ruptuur? Sportmedisch Wetenschappelijk Jaarcongres van de Vereniging voor Sportgeneeskunde (VSG), Ermelo, the Netherlands	2012	1.0
Bone mineral density changes following anterior cruciate ligament rupture. Annual congress of the Dutch Orthopaedic Association (NOV), Amsterdam, the Netherlands ***Awarded best clinical research and oral presentation, Biomet Award***	2013	1.0

Is radiological and functional recovery possible following anterior cruciate ligament rupture? Annual congress of the Dutch Arthroscopy Society (NVA), Den Bosch, the Netherlands	2013	1.0
Which predictors are related to degenerative changes of the knee following anterior cruciate ligament rupture? International Workshop on Osteoarthritis Imaging, Reykjavik, Island	2014	1.0
Vroege degeneratieve veranderingen in de knie na een voorste kruisband ruptuur. Sportmedisch Wetenschappelijk Jaarcongres van de Vereniging voor Sportgeneeskunde (VSG), Ermelo, the Netherlands	2014	1.0
Early degenerative changes in the knee two years after anterior cruciate ligament rupture. Annual congress of the Dutch Orthopaedic Association (NOV), Maastricht, the Netherlands	2015	1.0

Poster presentations

Identification of early degenerative changes of the knee after an anterior cruciate ligament lesion; the KNALL study. Osteoarthritis Research Society International, Brussels, Belgium	2010	1.0
Influence of determinants on the development of osteoarthritis in patients with an anterior cruciate ligament injury: a systematic review. Osteoarthritis Research Society International, San Diego, USA	2011	1.0
Degenerative changes five years after an anterior cruciate ligament rupture assessed by MOAKS. 6th International Workshop on Osteoarthritis Imaging combined with the OARSI OA Biomarkers Workshop III – Imaging Biomarker Validation and Qualification, Hilton Head, USA	2012	1.0
Which determinants predict osteoarthritis after an anterior cruciate ligament injury? A systematic review. World Sports Trauma Congress & European Federation of national Associations of Orthopaedic Sports Traumatology (EFOST) congress, London, United Kingdom	2012	1.0
Bone mineral density changes following anterior cruciate ligament rupture. Osteoarthritis Research Society International, Philadelphia, USA	2013	1.0

2. Teaching activities

Lecturing

Early degenerative changes after anterior cruciate ligament rupture; teaching physiotherapists	2009	0.6
KOOS or IKDC? Which questionnaire is most useful for monitoring patients with an anterior cruciate ligament injury? Clinimetrics, teaching orthopaedic surgeons and residents, Erasmus MC and MC Haaglanden.	2010	0.6
Which determinants predict osteoarthritis after anterior cruciate ligament rupture? Teaching orthopaedic surgeons and residents, Erasmus MC	2012	0.6
Statistics, teaching orthopaedic surgeons and residents, Erasmus MC	2013	0.6
The results of the KNALL study; Physiotherapist Symposium, MC Haaglanden	2013	0.6

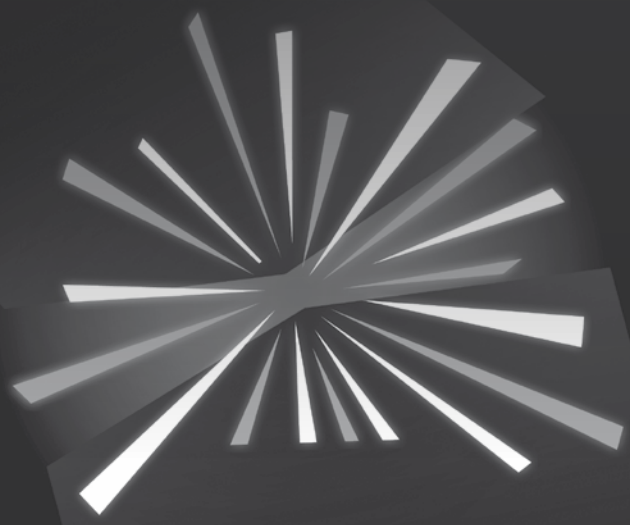
Supervising practicals and excursions, Tutoring

Minor Orthopaedics "Orthopaedic Sports Traumatology", third years medical students	2011 and 2012	0.6

Supervising Master's theses medical students

Are there any degenerative changes four to six years after an ACL injury? A.M. Witkamp	2010	3.0
The medical route of patients with an anterior cruciate ligament injury, G.W. Hendriks	2010	1.5
Degenerative changes four to six years after ACL injury, F.J. Schouten	2011	3.0
Bone mineral density changes in the knee after an anterior cruciate ligament rupture, W.A. van Eijsden	2012	3.0

List of publications



LIST OF PUBLICATIONS

van Meer BL, van de Port IGL, Schmikli SL, Backx FJG. Hoofdletsels in de hockeysport; registratie via een nieuw meldingsysteem. *Sport & Geneeskunde* 2009 (4):14-21.

van de Laar IMBH, van der Linde D, Oei EHG, Bos PK, Bessems JHJM, Bierma-Zeinstra SMA, **van Meer BL**, Pals G, Oldenburg RA, Bekkers JA et al. Phenotypic spectrum of the SMAD3-related aneurysms-osteoarthritis syndrome. *J Med Genet* 2012; 49(1):47-57.

van Meer BL, Meuffels DE, Vissers MM, Bierma-Zeinstra SMA, Verhaar JAN, Terwee CB, Reijman M. Knee Injury and Osteoarthritis Outcome Score or International Knee Documentation Committee Subjective Knee Form: which questionnaire is most useful to monitor patients with an anterior cruciate ligament rupture in the short term? *Arthroscopy* 2013; 29(4):701-715.

van Meer BL, Meuffels DE, Bierma-Zeinstra SMA, Reijman M, Terwee CB. Author's reply letter to the editor: Expert Panels: Can They Be Trusted? *Arthroscopy* 2013;29(7):1128.

van Meer BL, Waarsing JH, van Eijsden WA, Meuffels DE, van Arkel ER, Verhaar JA, Bierma-Zeinstra SM, Reijman M. Bone mineral density changes in the knee following anterior cruciate ligament rupture. *Osteoarthritis & Cartilage* 2014; 22(1):154-161.

Geraets SEW, Meuffels DE, **van Meer BL**, Breedveldt Boer HP, Bierma-Zeinstra SMA, Reijman M. Diagnostic value of medical history and physical examination of anterior cruciate ligament injury: a blinded study between primary care physician and orthopaedic surgeon. *Knee Surgery, Sports Traumatology, Arthroscopy*; Epub 2013 Nov 15.

Eggerding V, van Kuijk KSR, **van Meer BL**, Bierma-Zeinstra SMA, van Arkel ERA, Reijman M, Waarsing JH, Meuffels DE. Knee shape might predict clinical outcome after an ACL rupture. *Bone Joint J* 2014;96-B(6):737-742.

van Meer BL, Oei EHG, Bierma-Zeinstra SMA, van Arkel ERA, Verhaar JAN, Reijman M, Meuffels DE. Are magnetic resonance imaging recovery and laxity improvement possible after anterior cruciate ligament rupture in nonoperative treatment? *Arthroscopy* 2014;30(9):1092-1099.

Runhaar J, Schiphof D, **van Meer BL**, Reijman M, Bierma-Zeinstra SMA, Oei EHG. How to define subregional osteoarthritis progression using semi-quantitative MRI Osteoarthritis Knee Score (MOAKS). *Osteoarthritis & Cartilage* 2014;22(10):1533-1536.

van Meer BL, Meuffels DE, van Eijsden WA, Verhaar JAN, Bierma-Zeinstra SMA, Reijman M. Which determinants predict tibiofemoral and patellofemoral osteoarthritis after anterior cruciate ligament injury? A systematic review. Accepted in *Br J Sports Med.*

van Meer BL, Reijman M, Meuffels DE, van Arkel ERA, Verhaar JAN, Bierma-Zeinstra SMA, Oei EHG. Degenerative changes on MRI five years after non-operatively treated anterior cruciate ligament rupture. *Submitted.*

van Meer BL, Oei EHG, Meuffels DE, van Arkel ERA, Verhaar JAN, Bierma-Zeinstra SMA, Reijman M. Degenerative changes of the knee two years after anterior cruciate ligament rupture and related risk factors: a prospective observational follow-up study. *Submitted.*